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Volume 49 Number 57
January 197

CUK-H0G0T9-2-P25734

THE BRITISH JOURNAL OF RADIOLOGY

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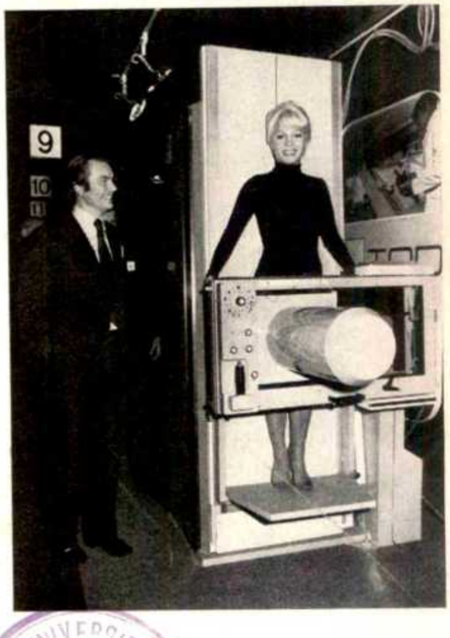

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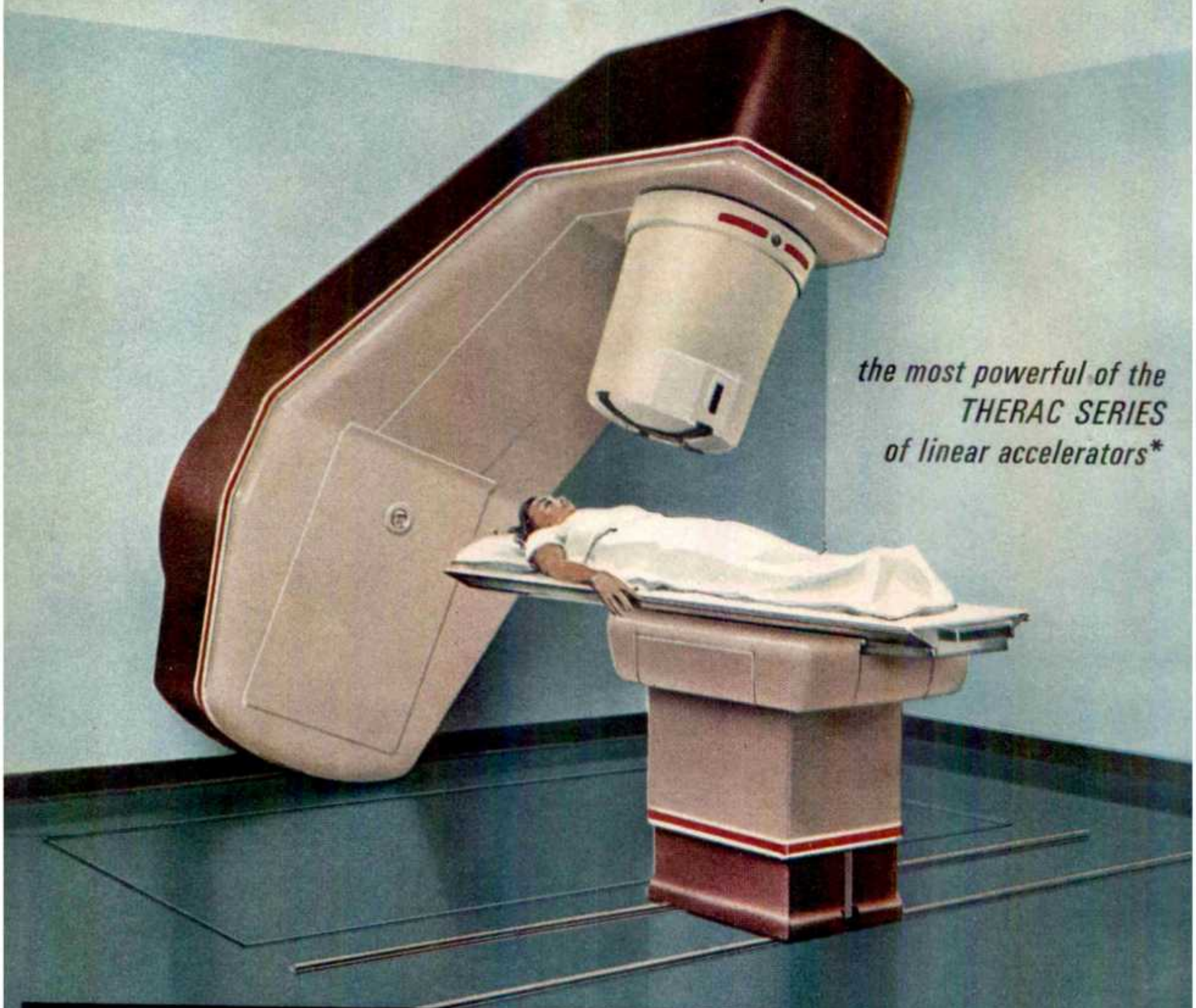

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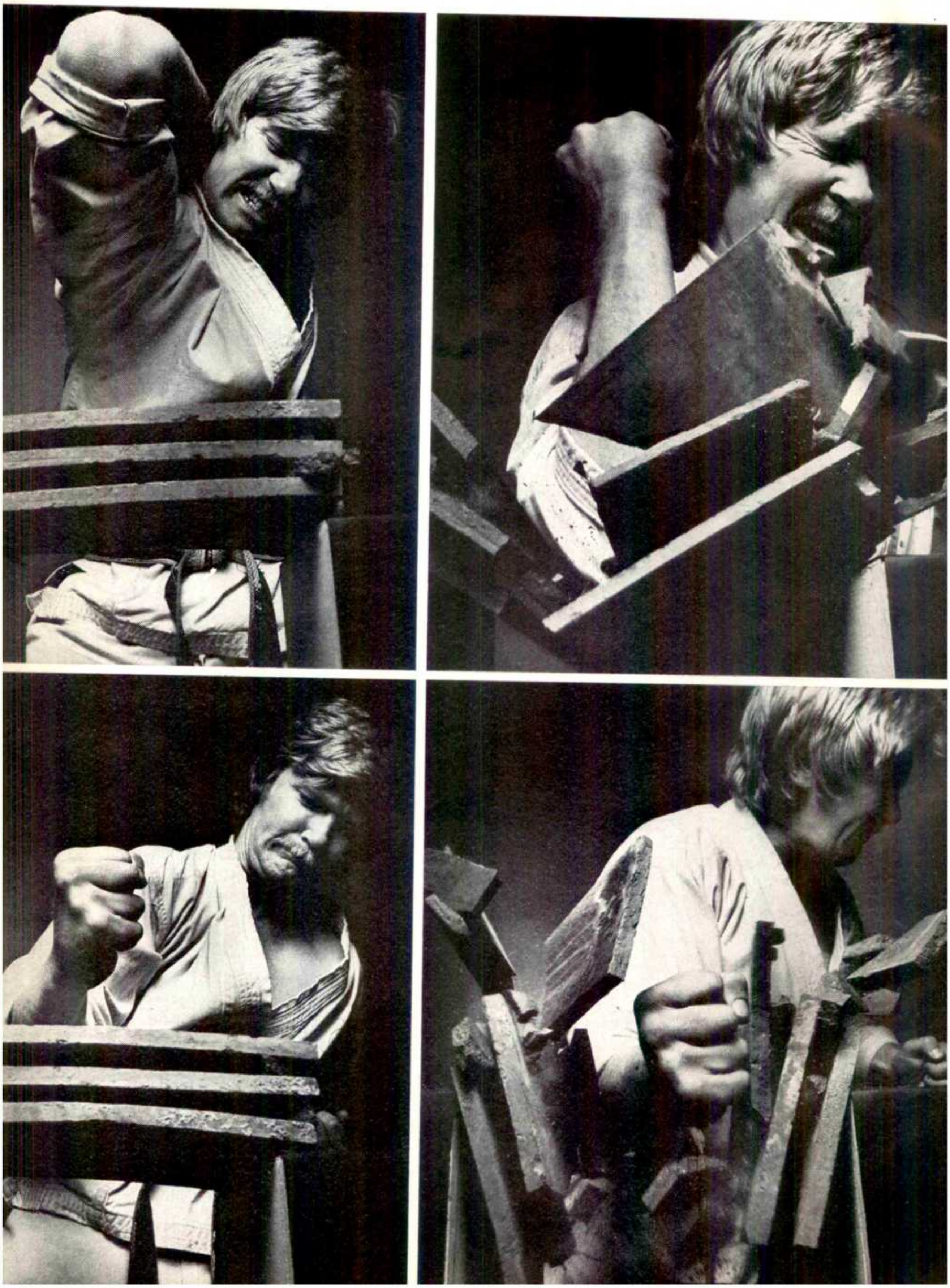

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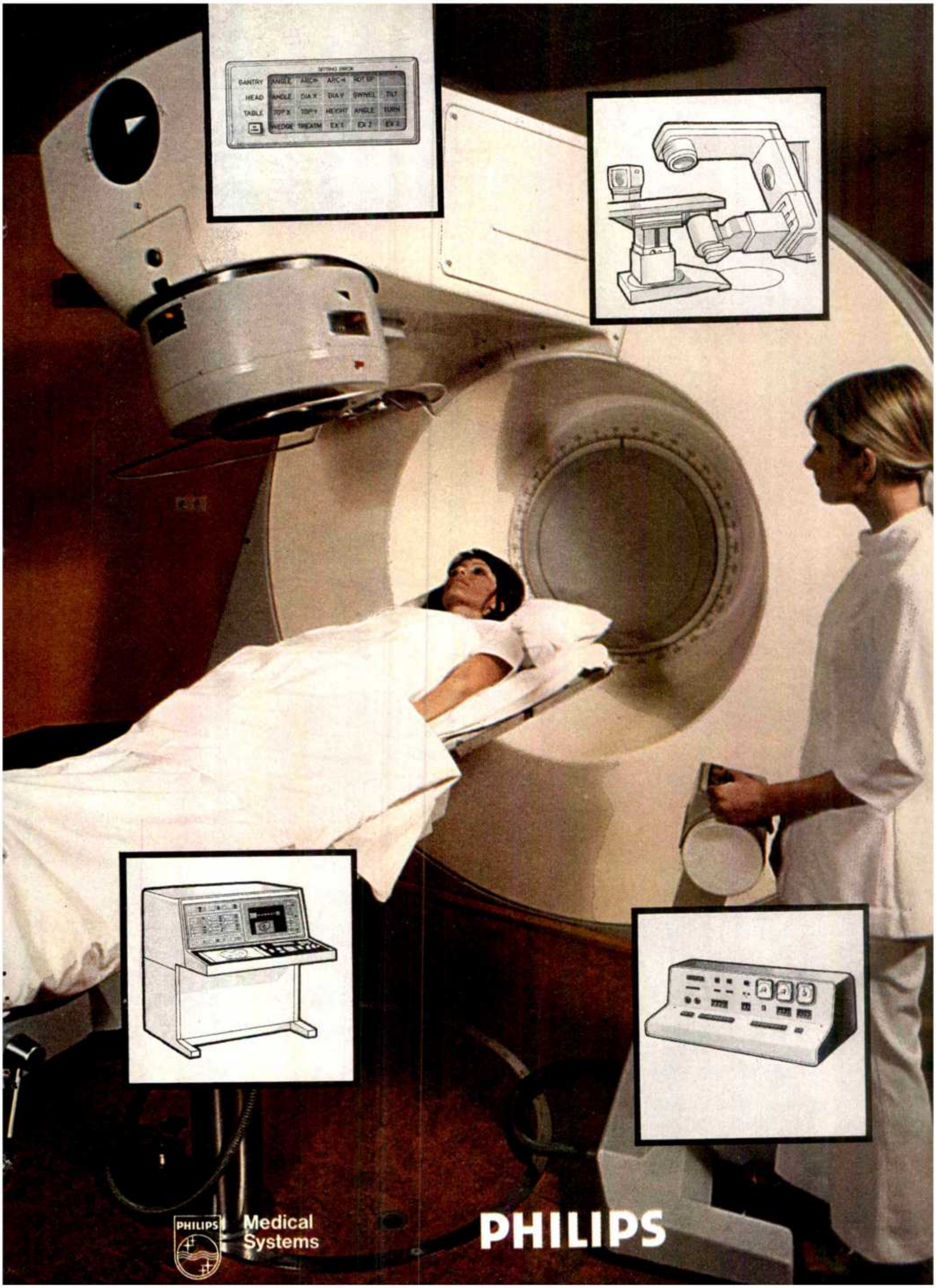
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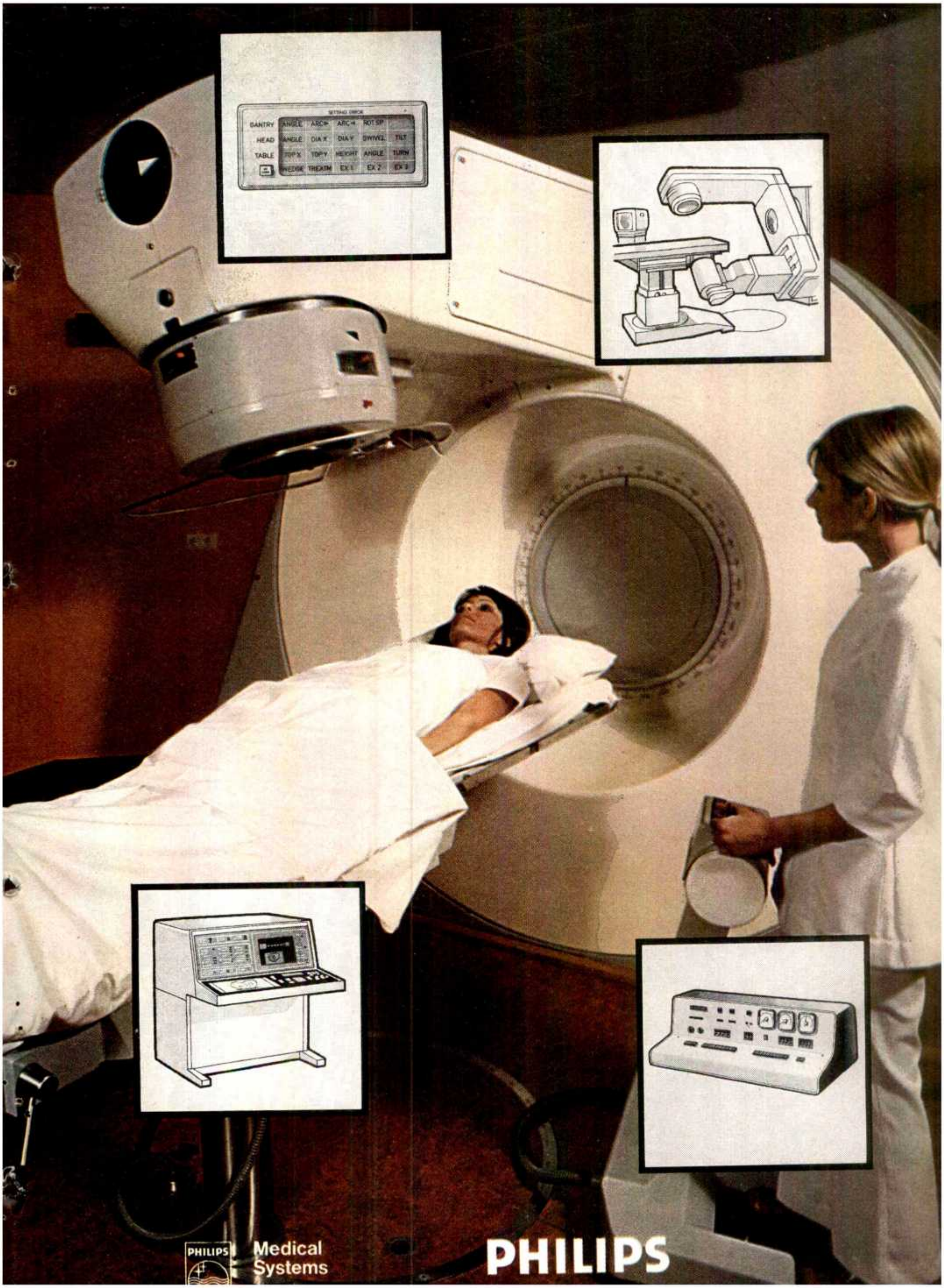
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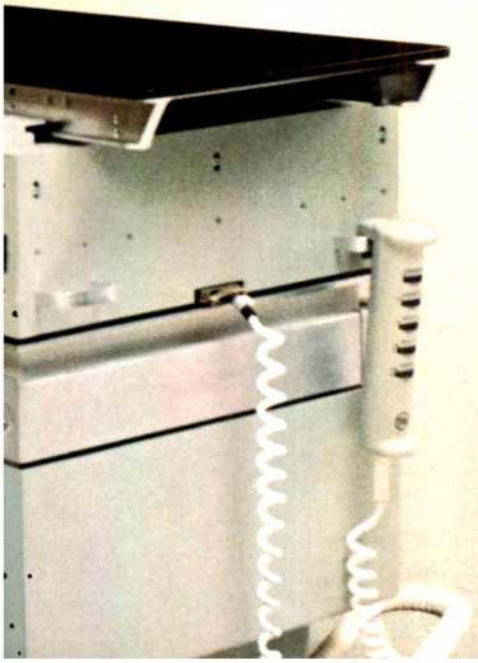

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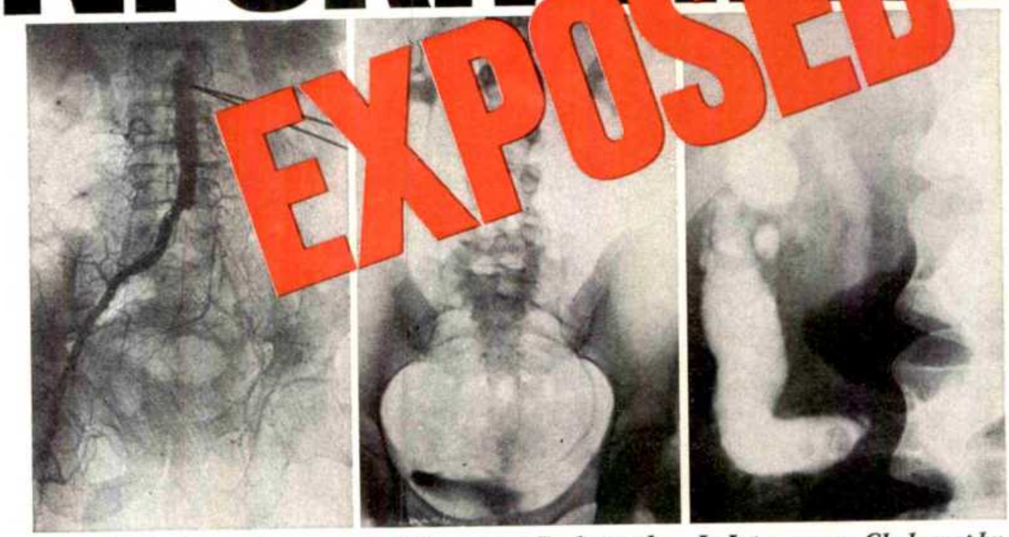

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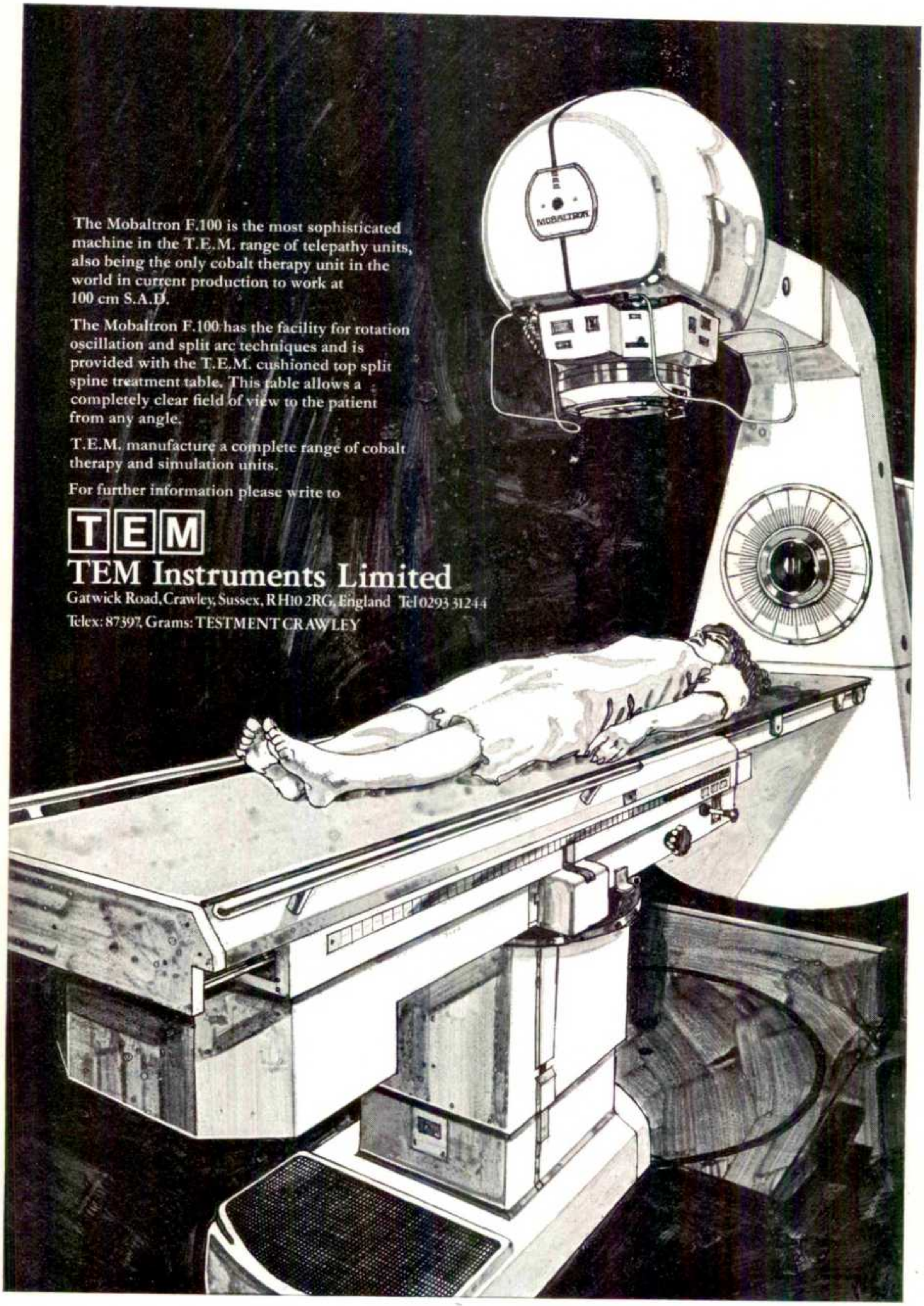

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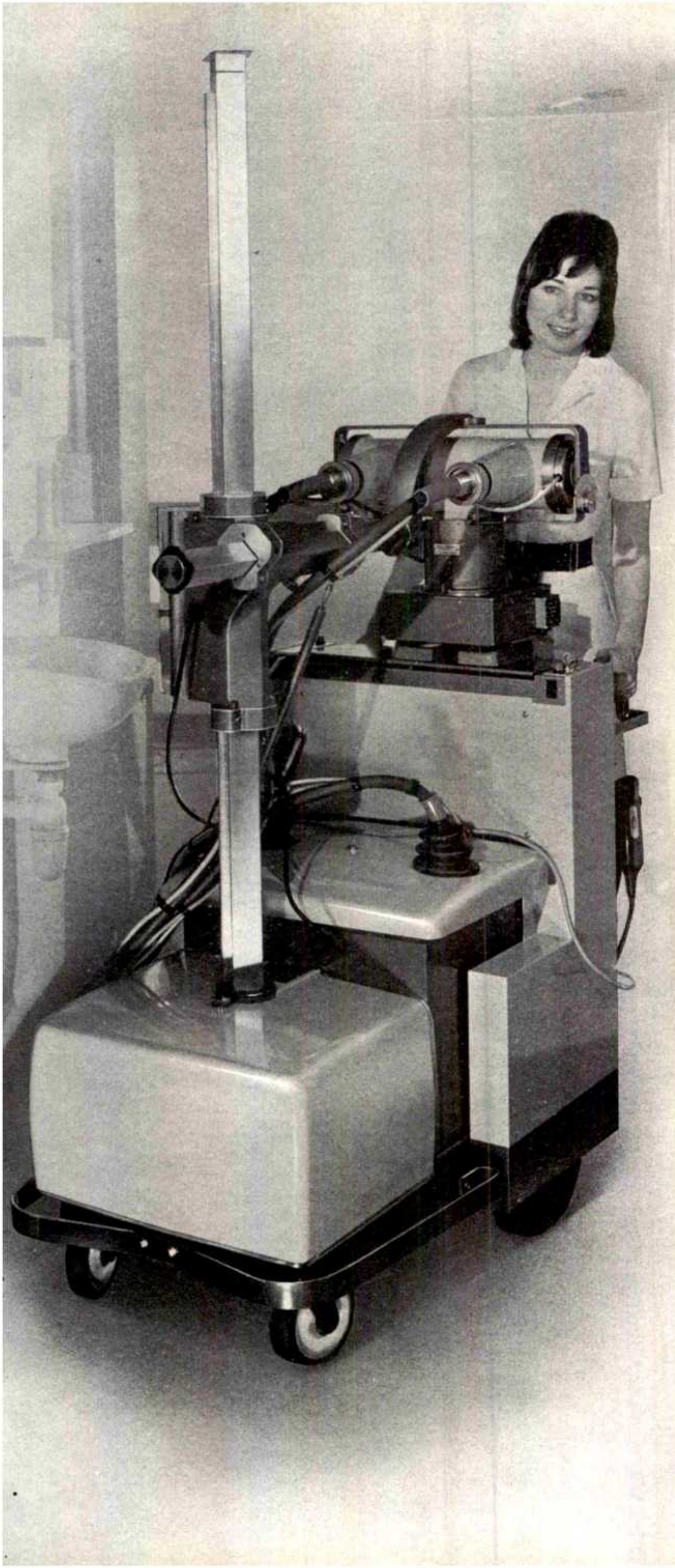

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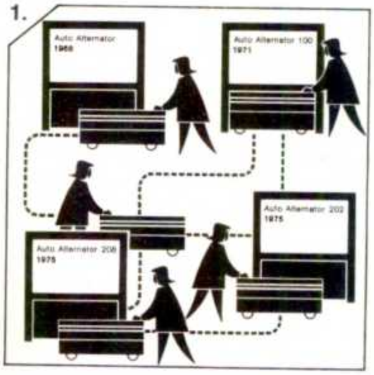

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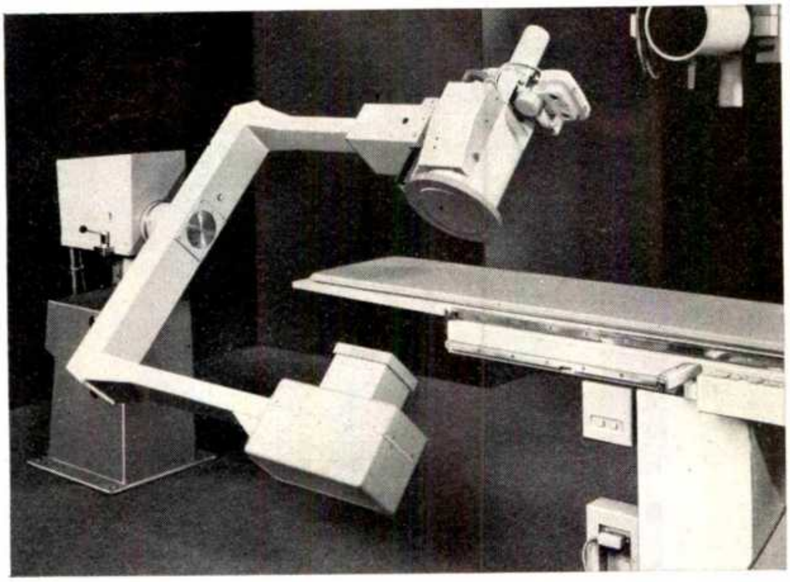

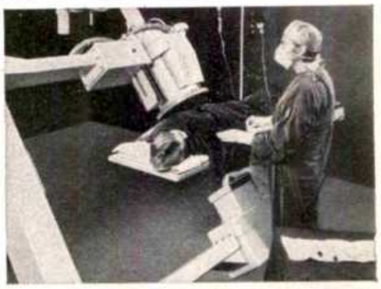

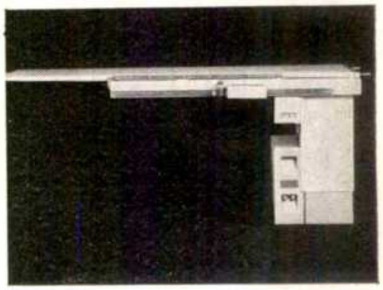

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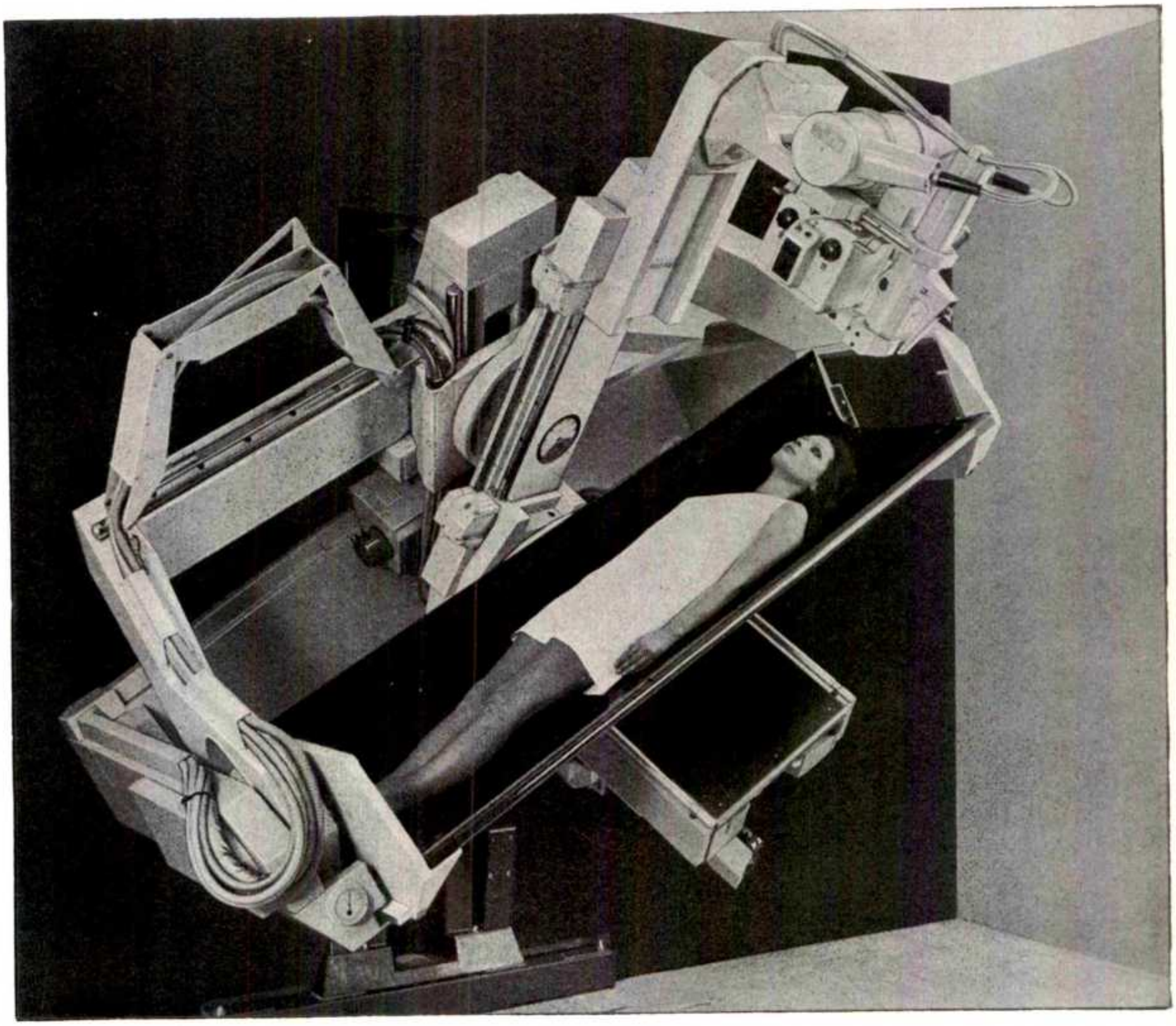

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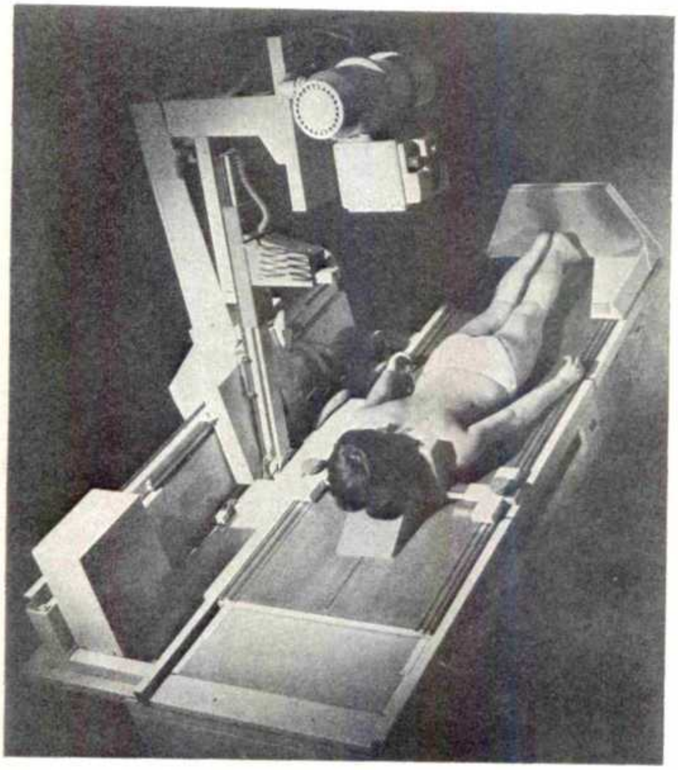

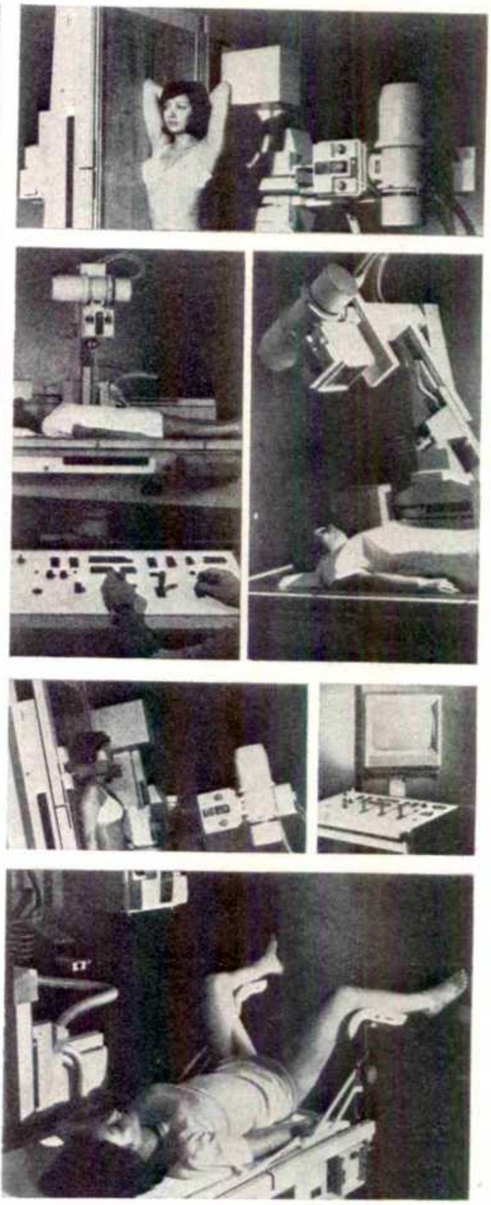

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Radiology now

Recent interest in the spleen

Radiology has played a part in the study of splenic function since Barcroft and his co-workers (Barcroft 1925; 1926; Barcroft *et al.*, 1925) observed the alteration of the size of the spleen in rabbits, cats and dogs by placing metallic sutures on the splenic capsule, and taking radiographs following various physiological stimuli. In clinical practice, plain-film radiography still has a place to surprise the unwary clinician. Development of isotope-labelling techniques followed later in the study of the relationship between cellular elements of the blood and splenic function. These methods are sometimes of great value, though scanning of the spleen has proved unreliable in the staging of Hodgkin's disease (Ell *et al.*, 1975).

Recently, Kreel (1974) has studied at length the incidence of aneurysms in the splenic arterial tree, using plain and contrast radiography *in vitro* and *in vivo*. He found an increasing incidence of aneurysms with age, as might be expected, but the female predominance is surprising. In his group with portal hypertension and splenomegaly, aneurysms were observed in a much younger age group. I am not sure that his hypothesis of "wear and tear from many years of high rates of blood flow" is well founded. Normally the splenic blood-flow rate, measured by clearance of radioactive xenon, is 120 ml./minute (Williams *et al.*, 1968), but this can rise markedly both in cirrhosis of the liver and haematological disorders. In splenomegaly due to myelofibrosis and leukaemia, splenic blood flow has been measured at 1·6 l./minute, representing over 20 per cent of the cardiac output (Garnet *et al.*, 1969). It would be interesting to observe the prevalence of aneurysms in patients with high splenic blood flow from causes other than portal hypertension.

Across the Atlantic, splenic arteriography is performed more readily than in this country in cases of suspected trauma to exclude rupture, haematoma and infarction. Here the detailed intra-splenic anatomy is important. However, the most exciting developments in the recent radiology of the spleen have come with the advances of modern immunology. The spleen is a secondary lymphoid organ, where lymphopoiesis begins late in fetal life, after the development of the thymus. Together with lymph-nodes, the spleen may respond to antigen stimulus by germinal centre and plasma cell production. Sandberg (1972) has used radioactive xenon to record an increase in intra-splenic blood flow following pertussis vaccination. This rather basic observation may in fact reveal a close link between vascular changes and immune responses or disorders in the spleen. Splenic atrophy has recently been shown to be associated with widespread immunological disturbances, notably auto-immunity (Wardrop *et al.*, 1975), Also, some splenic enlargement is reputed to occur after cardiac transplantation.

Herman, Yamamoto and Mellins (1972) investigated the micro-circulation changes of lymph-nodes during the primary immune response, and recently the same centre has turned its attention to the white pulp of the spleen. The marginal sinus of the splenic Malpighian follicle was recognized as a site of intimate contact between the reticulo-endothelial cells and the cellular elements in the blood many years ago (Macneal, Otani and Patterson, 1927). The localization of injected antigens near the marginal sinuses (Nossal *et al.*, 1966; Mitchell and Abbott, 1971), and the migration of antigen-binding cells from there to the germinal centre of the Malpighian follicle (Mitchell, 1972) are more recent findings. Concurrent work in radiological departments in Boston and London has demonstrated the finer vascular pathways of the white pulp using injection methods (Dubreuil *et al.*, 1975; Ayers *et al.*, 1975). The marginal sinus of the Malpighian follicle has been shown to be an important link in this pathway. Furthermore, the marginal sinuses have been seen *in vivo* in dogs by arteriography as round "haloes" of contrast, and the haemodynamics studied (Ayers *et al.*, 1975). The circulation through the marginal sinus has been shown to be slow. This, it is suggested, provides an environment which encourages the trans-vascular migration of cells to occur. Further studies may enable us to determine what changes occur in the microvascular structure and flow patterns during immune responses following antigen stimulus. Whether improving radiological techniques will allow such detail to be obtained in man *in vivo* has yet to be discovered. One could speculate that the unlikely combination of immunology and radiology may produce data in patients with immunological disturbances which will be useful in diagnosis and prognosis.

In clinical practice, advancement may come more quickly with the use of ultrasonography. This is already of value in the diagnosis of splenic cysts, and may prove its worth in the separation of splenic enlargement due to vascular engorgement from that due to increase in cellular content. Such tissue differentiation with ultrasonography is still in its early days: there are strong hopes for its success, but will the EMI scanner surpass all?

A. B. Ayers

REFERENCES

Ayers, A. B., Henry, K., Russell, S. B., and Steiner, R. E., 1976. The microvasculature of the spleen. *Clinical Radiology* (in press).

Barcroft, J., 1925. Recent knowledge of the spleen. *Lancet, 208*, 319–322.

1926. Some recent work on the functions of the spleen. *Lancet, 210*, 544–547.

Barcroft, J., Harris, H. A., Orahovats, D., and Weiss, R., 1925. A contribution to the physiology of the spleen. *Journal of Physiology (London), 60*, 443–456.

Dubreuil, A. E., Herman, P. G., Tilney, N. L., and Mellins, H. Z., 1975. Microangiography of the white pulp of the spleen. *American Journal of Roentgenology, 123*, 427–433.

Ell, P. J., Britton, K. E., Farrer-Brown, G., Keeling, D. H., Jelliffe, A. M., and Wood, T. P., 1975. An assessment of the value of spleen scanning in the staging of Hodgkin's disease. *British Journal of Radiology, 48*, 590–593.

Garnet, E. S., Goddard, B. A., Markby, D., and Webber, C. E., 1969. Spleen as an arterio-venous shunt. *Lancet, 1*, 386–388.

Herman, P. G., Yamamoto, I., and Mellins, H. Z., 1972. Blood circulation in the lymph node during primary immune response. *Journal of Experimental Medicine, 136*, 697–714.

Kreel, L., 1974. The recognition and incidence of splenic artery aneurysms, Part II–IV. *Australasian Radiology, 18*, 415–438.

MacNeal, W. J., Otani, S., and Patterson, M. B., 1927. The finer vascular channels of the spleen. *American Journal of Pathology, 3*, 111–122.

Mitchell, J., 1972. Antigens in immunity XVIII—The migration of antigen-binding, bone-marrow-derived and thymus-derived spleen cells in mice. *Immunology, 22*, 231–245.

Mitchell, J. and Abbott, A., 1971. Antigens in immunity XVI—A light and electron microscope study of antigen localization in the rat spleen. *Immunology, 21*, 207–224.

Nossal, G. J. V., Austin, C. M., Pye, J., and Mitchell, J., 1966. Antigens in immunity XII—Antigen trapping in the spleen. *International Archives of Allergy and Applied Immunology, 29*, 368–383.

Sandberg, G., 1972. Splenic blood flow in the guinea pig measured with xenon^{133} and calculation of venous output of lymphocytes. *Acta Physiologica Scandinavica, 84*, 208–216.

Wardrop, C. A. J., Lee, F. D., Dyet, J. F., Dagg., J. H., Singh, H., and Moffat, A., 1975. Immunological abnormalities in splenic atrophy. *Lancet, 2*, 4–7.

Williams, R., Condon, R. E., Williams, H. S., Blendis, L. M., and Kreel, L., 1968. Splenic blood flow in cirrhosis and portal hypertension. *Clinical Science, 34*, 441–452.

1975, *British Journal of Radiology*, *49*, 3–11

Radiological and histological findings in six patients with alpha-chain disease

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(*Received April, 1975*)

ABSTRACT

Detailed radiological and histological features of α-chain disease are presented against a background of the clinical and biochemical findings. The separation of this syndrome from other varieties of "Mediterranean" lymphoma is emphasized. The radiologist should in some instances be able to suggest the diagnosis in his differential diagnosis of abnormalities seen on examination of the small bowel. The histopathologist should be able to provide a diagnosis from examination of a peroral jejunal biopsy. One patient with this relatively uncommon disease had evidence of a hypertrophic osteoarthropathy. Two of the six patients had a transient episode of acute abdominal distension which resolved on conservative management.

The basic structure of immunoglobulin molecules is a pair of heavy polypeptide chains specific for each class of immunoglobulins (γ for Ig G, α for Ig A, μ for Ig M, etc.) combined with a pair of light chains, either κ or λ, common to all immunoglobulins (Fig. 1). In multiple myelomatosis, malignant plasma cells produce an excess of whole immunoglobulin molecules of a particular class and free light chains, or an excess of free light chains alone (Bence-Jones protein). In 1968, Seligmann and Rambaud described a patient with diffuse plasmacytosis of the small intestine in whom the plasma cells produced only part of the IgA molecule (Seligmann *et al.*, 1968; Rambaud *et al.*, 1968). This fragment contained parts of the two α chains (Fc fragment) but no light chains (Fig. 1). The condition was referred to as α-chain disease. It affects young adults and is characterized by diarrhoea, abdominal pain, loss of weight and finger clubbing. It occurs mainly in non-Europeans living in the Mediterranean region, but has also been described in patients from Pakistan, South Africa and South America (Doe *et al.*, 1970; Novis *et al.*, 1971; Seligmann, Mihaesco and Frangione, 1971). Fragments of the α chain of IgA have been identified in serum, urine and jejunal fluid. The purpose of this paper is to detail the radiological features in six patients suffering from α-chain disease and to relate these to the histylogical findings. The biochemical investigations and clinical findings in four of the six patients have been published in detail elsewhere (Doe *et al.*, 1972; Manousos *et al.*, 1974).

PATIENTS INVESTIGATED

Six males aged 18 to 36 years (mean 28) complained of weight loss and diarrhoea. Five complained of abdominal pain. One patient came from each of the following six countries: Pakistan, Bangladesh, Greece, Persia, Italy, and Turkey. Symptoms had been present for seven months to six years (mean two years eight months). Four were wasted, four showed gross finger clubbing and three had ankle oedema. None had detectable enlargement of

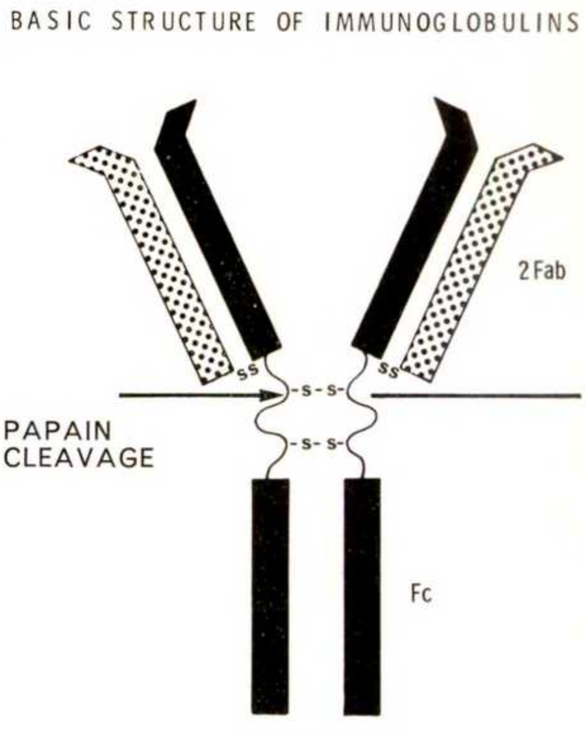

FIG. 1.

The paired heavy and light chains common to all antibody molecules. Enzymatic cleavage by papain yields an Fc fragment consisting of the terminal portions of both heavy chains free of light chains.

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liver, spleen or peripheral lymph-nodes. Five patients had moderate hypoalbuminaemia (serum albumin less than 3·5 g/100 ml.) and three had hypocalcaemia and hypomagnesaemia. One of these three had several episodes of tetany. Four patients had elevated serum levels of the intestinal isoenzyme of alkaline phosphatase. One had a marked increase in the bony isoenzyme of alkaline phosphatase. Malabsorption of fat was demonstrated in all patients. Malabsorption of D-xylose and vitamin B12 was exhibited by the five patients in whom these tests were performed. Using immunoselection plates in which electrophoresis into agarase containing anti-light-chain antisera precipitates all normal immunoglobulin, the presence of heavy chain fragments of Ig A free of light chains was demonstrated in the serum of all patients and in concentrated urine and jejunal fluid in three. These findings are characteristic of α-chain disease.

RADIOLOGY

In two patients, barium meal and follow-through examinations had been performed in other hospitals. In the remaining four, similar studies were carried out at Hammersmith Hospital using either Micropaque (Damancy and Co. Ltd.) or Baritop 100 (Sakai Chemical Industry Co. Ltd.). In one patient several barium studies were performed over a period of three years while he was on treatment. This patient was also investigated by lymphangiography which showed no abnormal lymph-nodes.

The radiological findings are summarized in Table I. Flocculation of the barium occurred to a minor degree in all six. Segmentation of the barium was a trivial feature in five, and not seen in one. All patients showed multiple fluid levels on erect films taken during the course of their follow-through examinations. The abnormalities were, in general, more severe in the proximal and mid-small bowel than in the distal small bowel. Circular folds were thickened to a minor extent in five patients and grossly thickened in the duodenum and proximal jejunum in one (Fig. 2, Patient 6). A nodular mucosal pattern was a striking feature in one (Fig. 3, Patient 3), prominent in two and present to a minor degree in two. Nodularity of the mucosal pattern was accompanied by the combination of a scalloped and spiky contour (Fig. 3) in three patients. All patients showed some evidence of segmental dilatation which was not constant with time (Fig. 4). Five patients showed inconstant narrowing of segments of small bowel. This feature was prominent in Patient 6 (Fig. 5). The findings in this patient

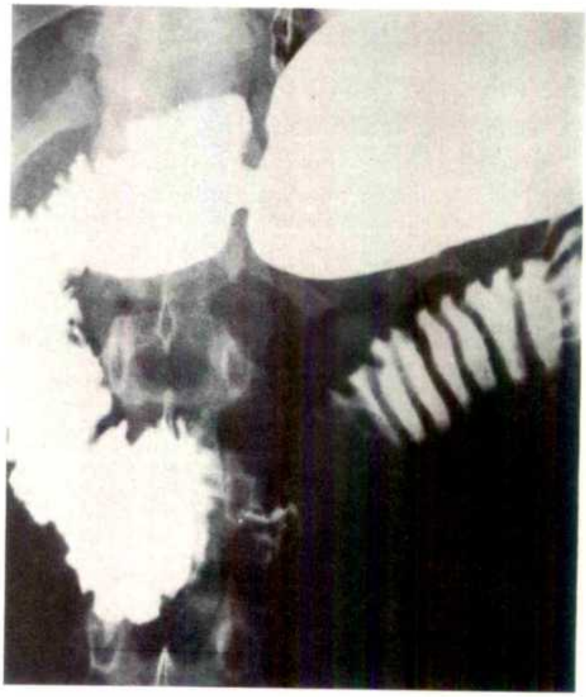


FIG. 2. *Patient 6.*

Supine radiograph of stomach, duodenum and proximal jejunum. Marked thickening of circular folds in distal duodenum and proximal jejunum. Coarse scalloping of the contour of first, second and third parts of the duodenum.

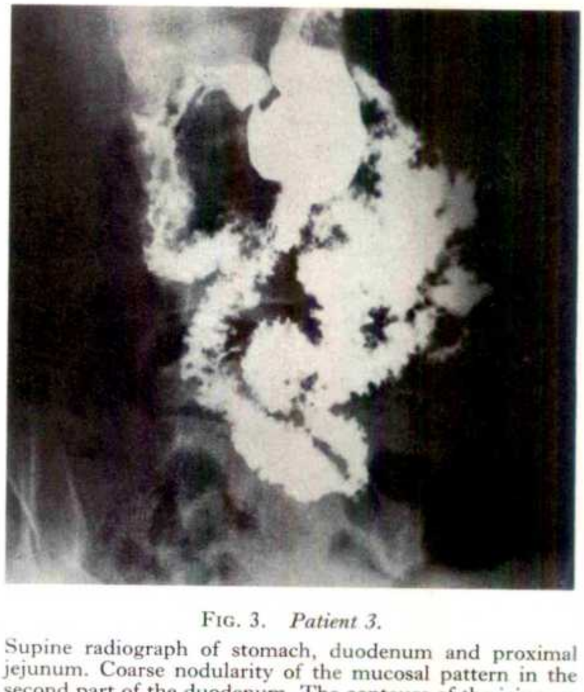


FIG. 3. *Patient 3.*

Supine radiograph of stomach, duodenum and proximal jejunum. Coarse nodularity of the mucosal pattern in the second part of the duodenum. The contours of the jejunum show a combination of scalloping with numerous fine projections or spikes of barium.

Radiological and histological findings in six patients with alpha-chain disease

TABLE I

	1 AH	2 LM	3 GS	4 ZY	5 GB	6 AK
Thick circular folds	+	+	+	+	+	+++
Nodular mucosal pattern	No	++	+++	+	++	+
Scalloped contour	No	Yes	Yes	No	Yes	Yes
Spiky contour	No	Yes	Yes	No	Yes	No
Inconstant segmental dilatation	+	+	++	+	+	++
Inconstant segmental narrowing "pseudo-stricture"	+	+	+	No	+	++
Localized "blow-outs" "pseudo-diverticula"	No	No	Yes	No	No	No
Fluid levels on erect radiographs	Yes	Yes	Yes	Yes	Yes	Yes
Episode of acute abdominal distension	No	No	Yes	No	No	Yes
Hypertrophic osteoarthropathy	No	No	Yes	No	Not assessed	No

Abnormality slight + moderate ++ severe +++

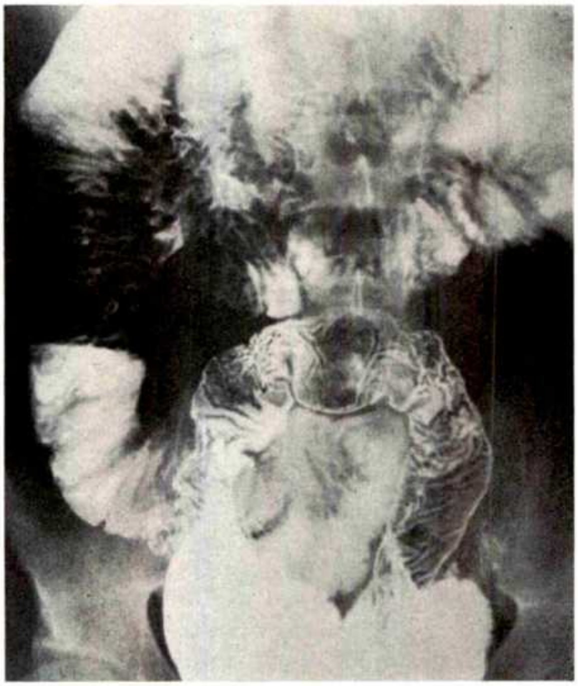


FIG. 4. *Patient 6.*

Supine radiograph of jejunum and ileum. Considerable dilatation of a loop of proximal ileum. This loop appeared undilated on a later radiograph. Moderate dilatation of some segments of jejunum and thickening of circular folds.

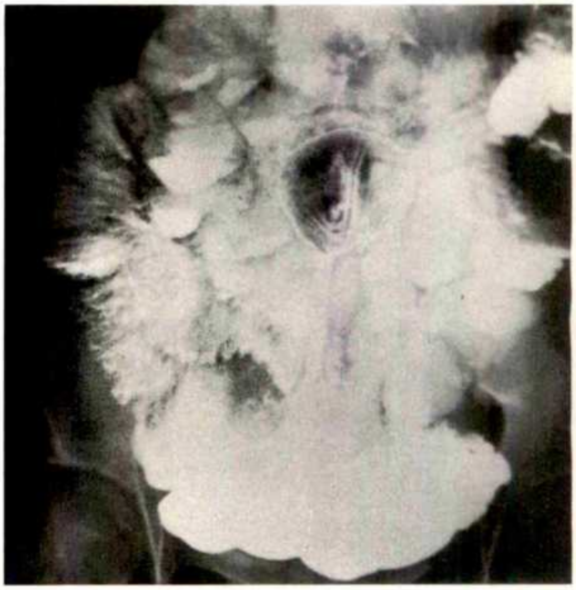


FIG. 5. *Patient 6.*

Erect radiograph of jejunum and ileum. Appreciable dilution of barium by fluid within the bowel and a few air-fluid levels. Short dilated segment of ileum just above the middle of the picture with a narrowed segment of bowel leading into and out of it. This narrowing was inconstant and may have been influenced by posture.

tended to make him stand out from the group. He was the only patient to show dilution of the barium by increased fluid within the bowel. Dilatation of small bowel was more obvious and more widespread in him than in any of the others. Patient 3 showed multiple pseudo-diverticula or localized "blow-outs" in the distal part of his mid-small bowel (Fig. 6). While under observation in hospital, Patients 3 and 6 had an episode of acute abdominal distension. Plain radiographs of the abdomen suggested the diagnosis of an ileus (Fig. 7) although bowel sounds were present. Both patients were treated by drip and suction and their abdominal distension resolved within two to three days. Patient 2 was followed for three years at Hammersmith Hospital from the time of presentation to the time of his death. His disease remitted for 18 months on treatment with cytotoxic agents and prednisone. His first barium

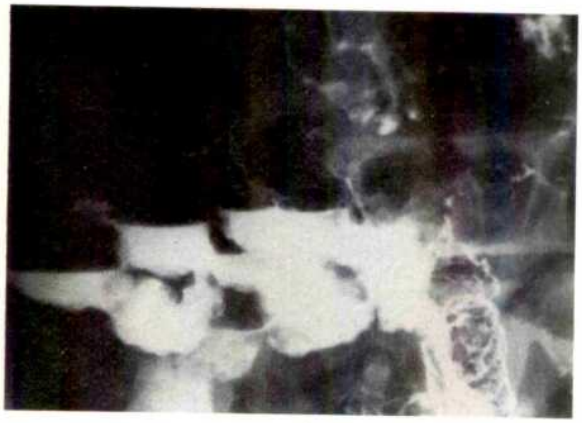


FIG. 6. *Patient 3.*
Erect radiograph of proximal ileum showing multiple "blow-outs" or "pseudo-diverticula" Air-fluid levels shown within the "blow-outs".

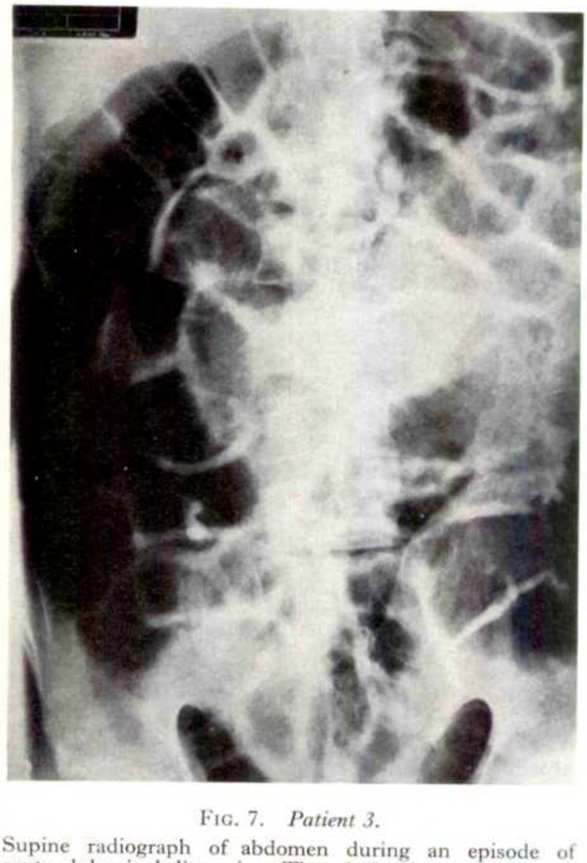


FIG. 7. *Patient 3.*
Supine radiograph of abdomen during an episode of acute abdominal distension. The whole of the small bowel and much of the colon is moderately distended by air. The degree of separation of the small bowel loops suggests considerable thickening of the wall of the small intestine. There was no clinical evidence of ascites. The distension resolved after a few days of treatment by drip and suction.

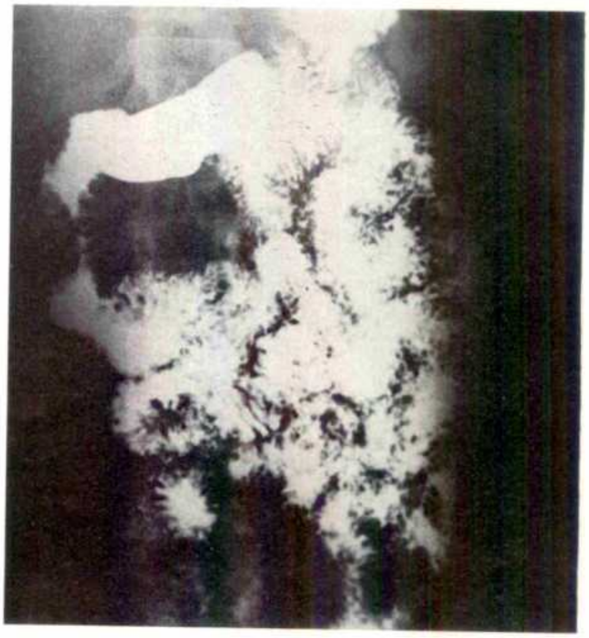


FIG. 8. *Patient 2.*
Supine radiograph of stomach, duodenum and jejunum when he first presented. Narrowing of the second part of the duodenum. The degree of narrowing was variable and was much less obvious in the prone position. The jejunum shows nodularity of mucosal pattern, the combination of scalloping and spikiness of its contours and thickening of circular folds.

meal and follow-through showed a relative narrowing of the second part of the duodenum (Fig. 8). In his final admission to hospital, he suffered from intractable vomiting. A barium meal showed a rigid stricture of the first and second parts of his duodenum with probable ulceration (Fig. 9).

One of the four patients with finger clubbing also had the features of hypertrophic osteoarthropathy. A skeletal survey showed periosteal new bone along the distal thirds of the shafts of his femora (Fig. 10). The bone isoenzyme of alkaline phosphatase was increased in his plasma. No bony abnormality was demonstrated in the other four patients in whom a skeletal survey was carried out.

HISTOLOGY

Peroral jejunal biopsies were obtained beyond the ligament of Treitz in all patients. The biopsy material was processed in the usual manner for light microscopy. Staining procedures included Haematoxylin and Eosin (H and E), the Periodic—

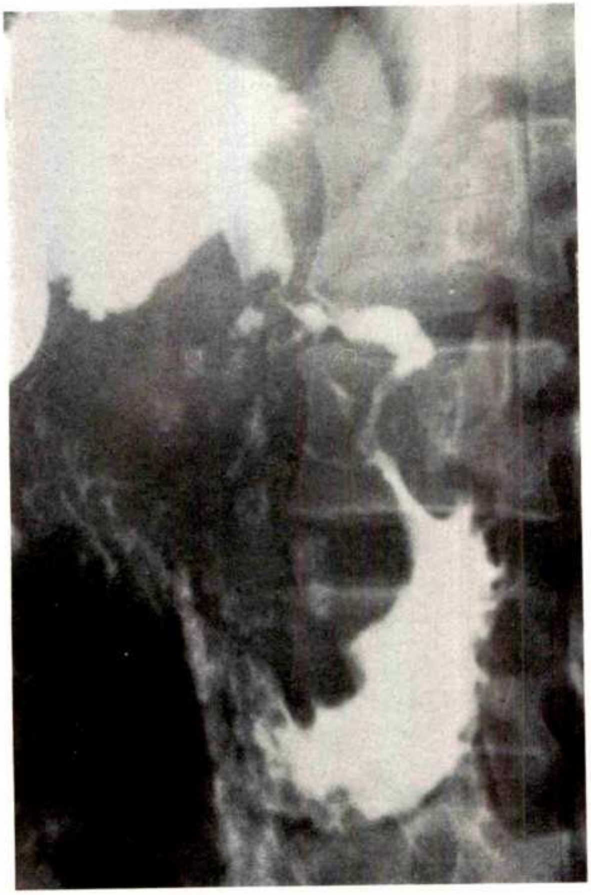


FIG. 9.

Prone-oblique radiograph of stomach and duodenum of Patient 2 when he presented terminally with intractable vomiting. Rigid stricture of first and second parts of the duodenum with probable ulceration. Contrast in para-ortic lymph-nodes from a previous lymphangiogram. Necropsy two weeks later showed an ulcerating tumour of the duodenum.

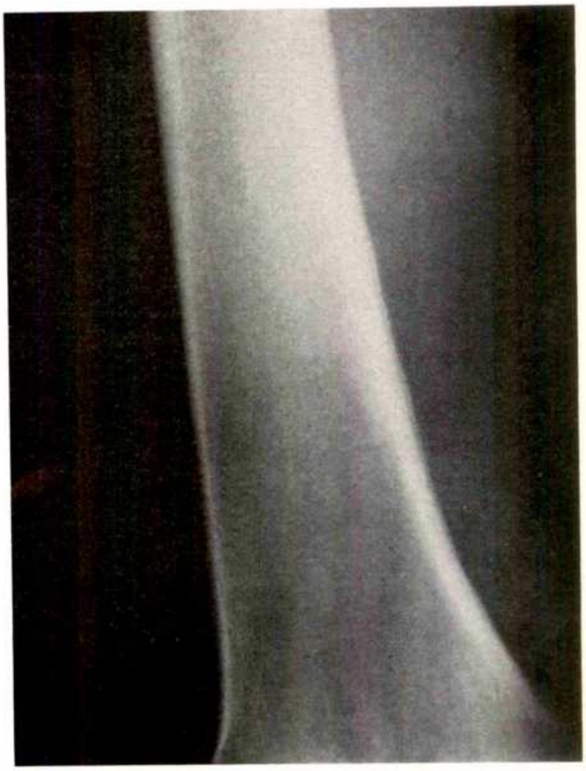


FIG. 10. *Patient 3.*

Antero-posterior radiograph of the distal part of the shaft of his right femur. Periosteal new bone formation shown along the medial margin of the shaft. Similar changes were present in the other femur and at the distal ends of both radii.

Acid—Schiff (PAS) sequence, methyl-green pyronine, and techniques for the demonstration of amyloid. Jejunal mucosa from five patients was also processed for ultrastructural studies.

Light microscopy

The main findings are summarized in Table II. The jejunal mucosa in all specimens presented a distinctive appearance. The basic abnormality was a massive and diffuse infiltration of the lamina propria with mononuclear cells. This resulted in thickening of mucosa, distortion of normal villous architecture, and wide separation of the crypts so that these structures appeared sparse (Fig. 11A). The abnormality of villous architecture consisted of widening and reduction in height so that there was a superficial resemblance to partial villous atrophy (PVA) and even subtotal villous atrophy (SVA). In contrast to coeliac disease and other conditions leading to PVA and SVA, the crypts were widely separated and few in number. The luminal epithelium showed a tendency to strip away from the underlying tissue. Where retained, it showed a relatively normal appearance with basal nuclei, distinct striate border and only a slight reduction in cell height.

The cellular infiltrate was predominantly plasma cell in type (Fig. 11B). In Patients 2, 5 and 6, the majority of cells were plasma cells with only occasional lymphocytes. The plasma cells were rather immature in Patient 2 but appeared well differentiated in Patients 5 and 6. In Patients 1 and 4, lymphocytes were more numerous and the plasma cells

TABLE II

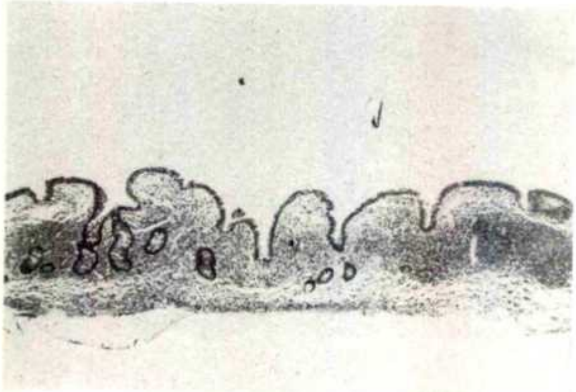
THE MORPHOLOGY OF THE JEJUNAL MUCOSA

Patient	Villi	Crypts	Plasma cell infiltrate	Luminal epithelium
1. AH	PVA	Moderate	Prominent diffuse	Low–normal
2. LM	SVA	Sparse	Massive diffuse	Low–normal
3. GS	SVA	Sparse	Massive diffuse	Low–normal
4. ZY	SVA	Sparse	Massive diffuse	Low–normal
5. GB	SVA	Sparse	Massive diffuse	Low–normal
6. AK	SVA	Sparse	Massive diffuse	Low–normal

PVA—Partial villous atrophy; SVA—Subtotal villous atrophy.

appeared mature. In Patient 3, a larger proportion of cells were intermediate between lymphocytes and plasma cells. In all patients most of the plasma cells exhibited cytoplasmic pyroninophilia, lacked any significant degree of mitotic activity and did not show atypical or multinucleated forms. Eosinophils were prominent in Patient 1. A remarkable infiltration of the luminal epithelium with lymphocytes was observed only in Patient 4. Because of the superficial nature of the peroral biopsies, the presence or absence of invasion of the submucosa could not be assessed.

Patient 2 responded initially to therapy, but relapsed with evidence of intestinal and bile-duct obstruction. Laparotomy revealed malignant obstruction of the duodenum and common bile-duct and an ileo-ileal intussusception. At post-mortem the duodenum was the site of an ulcerating tumour. Distal to this the mucosa showed a diffusely thickened, almost cobblestone appearance. Numerous polypoid tumours were found throughout the gut from the jejunum to the rectum. They varied in diameter from a few mm to 5 cm, the largest one being in the rectum. These tumours were composed of large pyroninophilic lymphoid cells with evidence or differentiation to the plasma cell series, an observation confirmed by ultrastructural studies. While these tumours were clearly of plasma cell origin, the cells were much more primitive and neoplastic in appearance than those seen in the initial jejunal biopsy.



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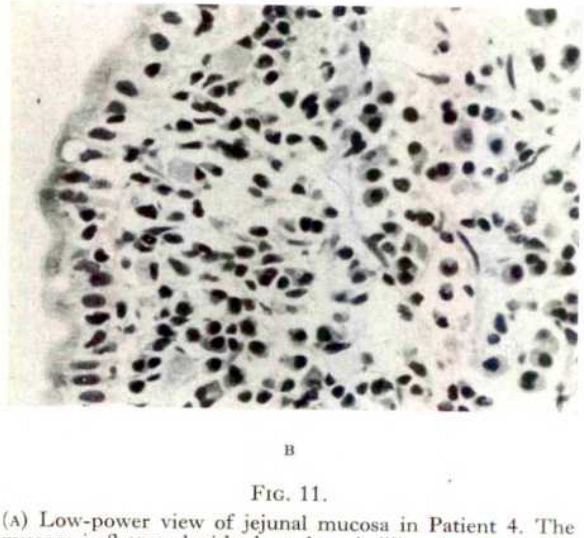


B

Fig. 11.

(A) Low-power view of jejunal mucosa in Patient 4. The mucosa is flattened with short, broad villi and reduction in the number of crypts. The lamina propria is occupied by a dense cellular infiltrate.

(B) High-power view (× 200) showing the plasma cell nature of the infiltrating cells. Note the relatively normal surface epithelium on the left.

Electron microscopy

Ultrastructural studies performed in five of the six patients, confirmed the essential normality of the surface epithelium. The majority of infiltrating cells showed the cytoplasmic and nuclear structure of plasma cells (Doe *et al.*, 1972). Most were round, with round to oval, regularly contoured nuclei.

TABLE I

TECHNICAL DETAILS OF THE X-RAY TUBES

Type	Filtration (mm.Al)		Focus-detector distance (cm)	Focal spot size (mm)	Applied tube voltages (kVp)
	Inherent	Added			
1. Siemen's "Mammomat" (Rotating Molybdenum Anode)	Be. window	30 μm Mo	45 and 183 cm	0·6×0·6	28, 30, 45 and 50 (constant potential generator)
2. Siemen's (Rotating Tungsten Anode)	Glass window	0·5 mm Al	83 cm	0·6×0·6	35 and 50 (constant potential generator)

TABLE II

DETAILS OF THE THREE DETECTING SYSTEMS

Type	Processor	Processing time, minutes
1. Non-screen film Kodak PE 4006	Kodak automatic	1·5
2. Medichrome film; vacuum packed with one intensifying screen	Automatic with special chemicals	2·5
3. Selenium plate – xeroradiography vide:—Gillbe P., 1973	Xerox "125" system	1·5

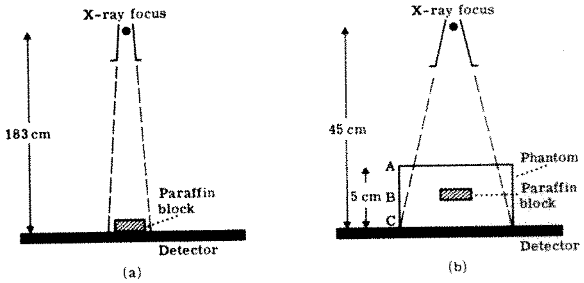


FIG. 1.

The geometry employed to radiograph the paraffin blocks. The "Mammomat" (See Table I) was used with the three detecting systems described in Table II. (A) In air at 183 cm. (B) In phantom at 45 cm. The block is shown in the middle of the phantom at level "B": radiography was repeated with the block positioned at levels "A" and "C".

arrangements shown in Fig. 1. The set up, illustrated in Fig. 1A, was chosen to minimize the effects of focal spot dimensions and magnification, and thereby to provide radiological images of optimum quality. Each radiograph was viewed through an optical microscope fitted with a graduated eye-piece micrometer, and the "sizes" of the radiological images of the calcifications were measured. ("Size" is defined as the greatest linear dimension of each particle, corrected for magnification due to projection.) The best radiographs were selected for each block to enable the measurements of size to be made as a key for the comparison of subsequent radiographs. The blocks were placed within a phantom consisting of polythene sheets (15×15×0·5 cm) to simulate fatty breast tissue, and radiographed with the geometry shown in Fig. 1B which more closely resembles clinical conditions in which the calcification may be separated from the detector by the scattering medium. The processed radiographs were inspected by a number of observers (never less than five people with appropriate experience) who recorded the position of each particle that they could see. By relating these observations to the corresponding key radiograph, the minimum size detected by each person was determined, and by taking the mean of those measured for all observers the "threshold size" established.

Each person also indicated whether one radiograph was of "better" or "worse" quality than another. Although such terms are virtually impossible to define, they are of value in practice, since the judgement is compounded of several impressions such as resolution, contrast pattern, etc. and is relevant to the decisions that have to be made in radiology. In the discussions below it is referred to as image quality.

To determine the influence of breast architecture on the detection of calcifications, experiments were repeated using six suitable mastectomy specimens in place of the simple phantom shown in Fig. 1B. One of the specimens containing a very wide range of calcification sizes was further radiographed with the tungsten anode X-ray tube to assess the effect of the harder radiation on image quality. Details of this equipment are given in Table I. For reasons which are stressed below, studies with these specimens were limited to the use of non-screen film and xeroradiography.

Throughout this work, great care was taken to use optimum exposure conditions, and to eliminate errors due to under- and over-exposure, by obtaining a series of radiographs on each detecting system for every change in radiological or geometrical parameter.

RESULTS

The radiographs taken with the geometry shown in Fig. 1A gave values of "threshold" of approximately 100 μm for each of the detecting systems at all available tube voltages. The image quality obtained with Medichrome and PE 4006 deteriorated with an increased tube voltage, while the effect was hardly noticeable in xeroradiography.

With the arrangement indicated in Fig. 1B, several important facts were established concerning the "threshold" size (defined above).

(1) The variations in the positions of the paraffin blocks, illustrated as A, B and C in Fig. 1B did not affect any of the "threshold" values measured on the three radiographic systems.

(2) At 28 and 30 kVp the "threshold" for xeroradiography was approximately 100 μm, while the values for both Medichrome and PE 4006 film were raised to 400 μm.

(3) When film techniques were used, increasing the voltage above 30 kVp led to a rapid loss in film quality due to the scatter arising from the configuration shown in Fig. 1B. For xeroradiography, however, the threshold values remained at 100 μm although the image quality showed some deterioration.

(4) No measurable differences were found between the PE 4006 and Medichrome films throughout these experiments and therefore the examinations of the six mastectomy specimens were confined to the uses of PE 4006 film and xeroradiography.

Comparative studies of the conventional radiographs and xeroradiographs of the breast specimens confirmed "threshold" values of approximately 400 μm and 100 μm respectively, and clearly demonstrated the value of the "edge" effect of xeroradiography. The comparatively large exposure latitude of the xeroradiographic plate and the edge effect combine to give better detection of calcifications both when it is sparse and when it is found in areas such as the subareolar region where increased attenuation causes pronounced opacity in film techniques. Results obtained with the mastectomy specimens did not differ significantly from those obtained with the paraffin blocks embedded in the phantom.

The xeroradiographs of the mastectomy specimen, taken with the tungsten target X-ray tube, using the same projection as that employed with the molybdenum tube showed:—

(1) xeroradiographs taken with the tungsten anode did not alter the "threshold" values although they were of reduced contrast;

(2) increases in applied tube voltage had small effect on xeroradiography, but resulted in severe deterioration of the image quality of the film;

(3) all conventional radiographs taken with the tungsten tube (used in our technique) were considered to be of "unacceptable quality" for clinical work.

Part II: The correlation between radiological and pathological findings and their significance in malignant and benign disease

MATERIALS AND METHODS

During the six-month period of this study, 68 patients with carcinoma of the breast and 135 patients with benign breast disease who were treated by surgery had pre-operative mammograms. The 68 cases of carcinoma, together with 27 patients with benign breast disease in whom calcification was considered a significant radiological abnormality, were studied in detail. Cases with extremely sparse and widespread calcification, the distinctive large calcifications of a fibroadenoma or the typical round and ring-like calcifications occurring in duct ectasia, were not included. Xeroradiographs were taken of a high proportion of the malignant surgical specimens and of all benign biopsy specimens. Stereoscopic views were taken of selected specimens (Boag, Stacey and Davis, 1971; 1972). Histology was available for all cases.

Where calcification was the only basis for biopsy, the surgical specimen was xeroradiographed prior to pathological examination, and a frozen section only performed on an obvious tumour. When no obvious dominant abnormal area was seen or felt, multiple tissue blocks were taken for permanent paraffin sections. All specimens were fixed and processed routinely. Three blocks were taken from each grossly obvious carcinoma, and multiple blocks from the other specimens. Special stains were performed when considered appropriate, a Von Kossa stain for calcium salts being performed on one section from each carcinoma.

If the amount of calcification seen on the histology slides was significantly less than demonstrated on the xeroradiograph, further tissue was examined. In order to locate the calcification, blocks and reserve tissue were subjected to further radiological examination.

The following features of the calcification seen on the pre-operative mammograms were noted:

(1) the presence or absence of a mass;
(2) the appearance of the mass;
(3) the location of the calcification in relationship to the mass;
(4) the size, number and spatial distribution of the calcifications within the breast.

The size of the calcification particles was measured using a graduated micrometer eye-piece and a dissecting microscope. For those of irregular shape the greatest linear dimension was recorded. The approximate range of size of the particles seen on both projections was recorded for each patient. Particles over 1,000 μm were considered coarse, those between 500 μm and 1,000 μm intermediate, and those less than 500 μm fine. The distribution of the calcification was often difficult to determine. An attempt was made to note, using both views, whether they were closely packed within a small or large area or widespread within a quadrant, or scattered over the entire breast.

The following histological features of all the carcinomas (both with and without calcification) and the benign lesions containing calcification were noted where relevant:

(1) the histological diagnosis of the associated lesion including the type and grade of carcinoma (Bloom and Richardson, 1957);
(2) the pathological size of the tumour and the number of involved axillary lymph-nodes;
(3) the histological site and the size of the particles.

The latter was measured using an eye-piece micrometer, and the greatest linear dimension recorded. Size was difficult to assess since in some cases many small particles were clustered closely together; and the aggregate was then measured; in addition, larger deposits were often shattered during the process of section cutting.

Results have been tabulated wherever possible.

RESULTS

Incidence of calcification in carcinomas and benign breast disease

Calcification was found in the region of the tumour in 33 of 68 pre-operative mammograms of patients with carcinoma of the breast, an incidence of 48·5 per cent. In ten additional cases in which calcification was not seen on the pre-operative mammogram, it was found in histological sections, bringing the overall incidence of calcification in this series to 63 per cent.

Xeroradiographs of the operation specimen which contained the carcinoma were available for 20 of the 33 cases in which calcification was seen on the pre-operative mammogram. Although the calcification was more easily demonstrated, no significant additional amount was seen (Fig. 2A).

The presence of calcification was confirmed on histology in all but two cases: in each of these two exceptions only two or three small particles had been visible on the pre-operative mammogram.

Calcification was *not* seen in the pre-operative mammograms of 35 cases of carcinoma. Xeroradiographs of 22 of these operation specimens containing the carcinoma were available for study, but calcification could not be demonstrated even in the ten cases in which calcification was found on histology sections.

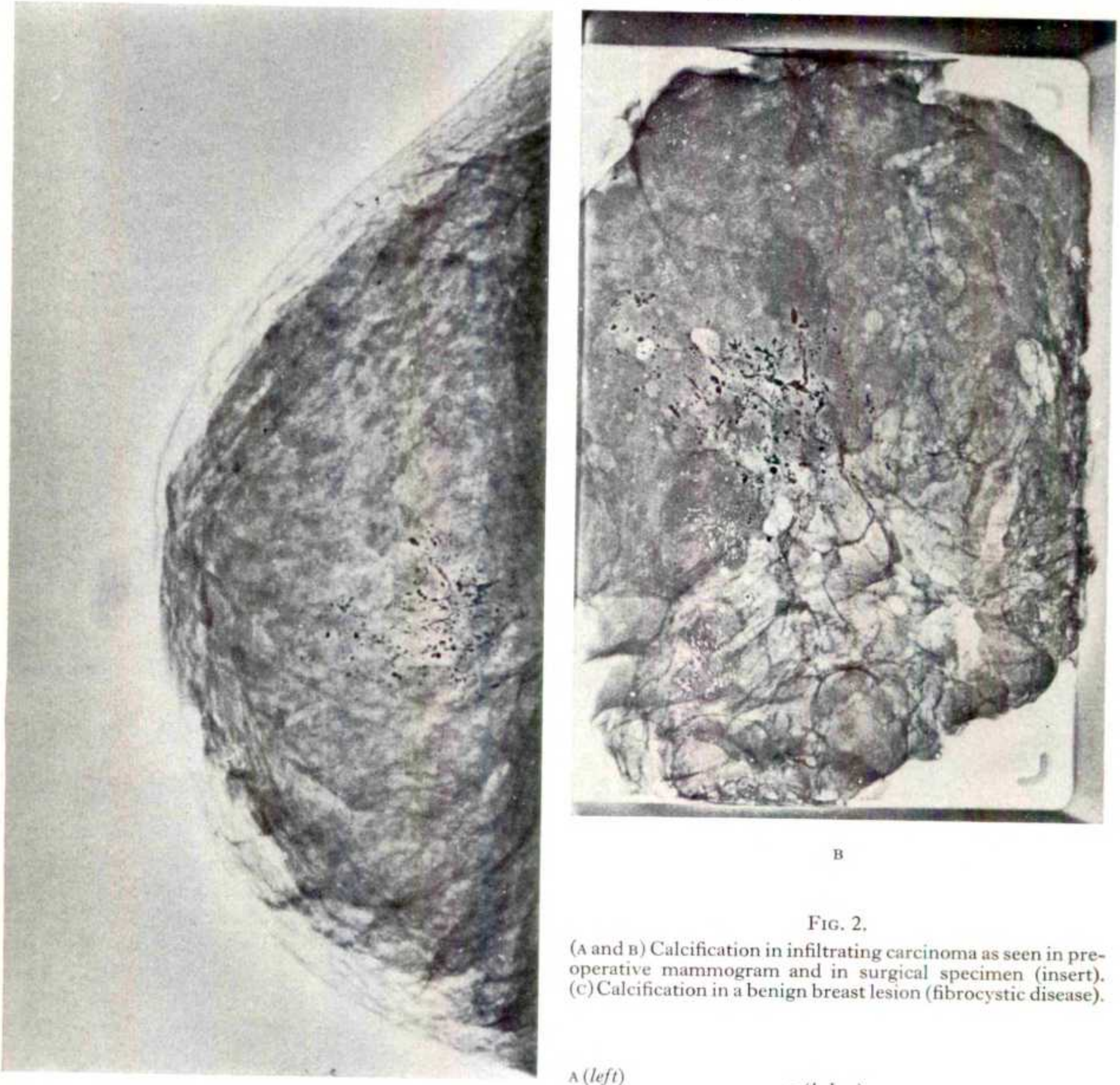
Calcification was seen as a significant abnormality on the pre-operative mammograms of 27 of the 135 patients who had benign breast disease on biopsy (20 per cent). Specimen radiography in this benign group did not reveal additional evidence of calcification.

Clinical and radiological features of carcinomas and benign breasts containing calcification

A summary of the clinical features and the appearances of the pre-operative mammograms from the patients with both malignant and benign breast lesions in which calcification was seen, are shown in Tables III–VII.

1. *Relationship of calcification to other radiological features*

Table III shows that in 14 cases of carcinoma, calcification was the only radiological abnormality, although a definite clinical mass was palpable in four of these patients. However, in 19 other patients with carcinoma with a clinically palpable lump, a mass was demonstrated radiologically. In seven of the latter cases the presence of calcification contributed to the



B

Fig. 2.

(A and B) Calcification in infiltrating carcinoma as seen in pre-operative mammogram and in surgical specimen (insert). (C) Calcification in a benign breast lesion (fibrocystic disease).

A (*left*)

C (*below*)

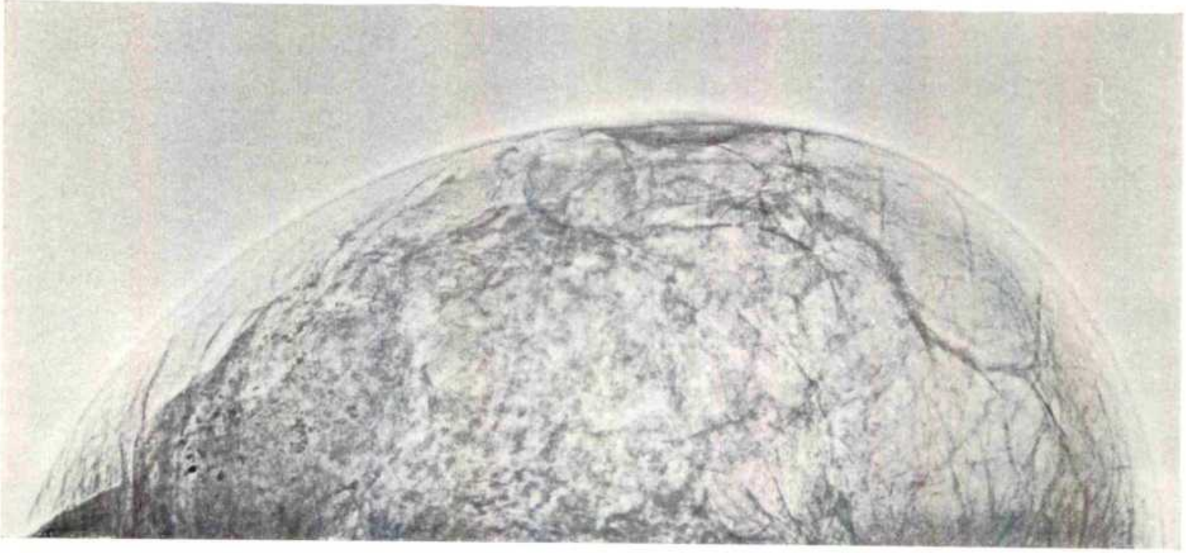


TABLE III

CLINICAL AND RADIOLOGICAL FINDINGS OTHER THAN CALCIFICATION ON THE PRE-OPERATIVE MAMMOGRAMS OF PATIENTS WITH CARCINOMA AND BENIGN BREAST LESIONS

Clinical findings	Radiological findings other than calcification					
	Mass or disturbed architecture		No other abnormality		Total	
	Carcinomas	Benign lesions	Carcinomas	Benign lesions	Carcinomas	Benign lesions
Palpable mass	19	6	4	4	23	10
Palpable nodularity, no definite mass	0	2	6	8	6	10
Nipple discharge no palpable abnormality	0	0	0	1	0	1
Tenderness no palpable abnormality	0	1	0	0	0	1
No palpable or other abnormality	0	1	4	4	4	5
Total	19	10	14	17	33	27

TABLE IV

SPATIAL RELATIONSHIP OF CALCIFICATION TO OTHER RADIOLOGICAL ABNORMALITIES ON PRE-OPERATIVE MAMMOGRAMS OF PATIENTS WITH CARCINOMA AND BENIGN BREAST LESION

Site of calcification	Carcinoma	Benign
Calcification only within mass or area of disturbed architecture	11	7
Calcification within mass or area of disturbed architecture and surrounding tissue	9	2
Calcification seen only in surrounding tissue	0	1
Calcification unaccompanied by mass or area of disturbed architecture	13	17
Total	33	27

TABLE V

SIZE OF CALCIFICATIONS ON PRE-OPERATIVE MAMMOGRAMS OF PATIENTS WITH CARCINOMA AND BENIGN BREAST LESIONS

Size of the majority of calcifications	Carcinomas	Benign lesions
1. Less than 500 μm	11	9
2. Between 500 μm and 900 μm	15*	12†
3. A mixture of 1 and 2 above	5	4
4. More than 1,000 μm	2	2
Total	33	27

* 13 of these cases contained some fine calcification less than 500 μm.

† 3 of these cases contained some fine calcification less than 500 μm.

radiological diagnosis of carcinoma; in five the appearance of the mass was equivocal; in two the mass alone would have been considered benign. In 12 cases the radiological appearance of the mass was diagnostic of a carcinoma, the presence of calcification being merely confirmatory.

The spatial relationship of calcification to the mass when present is shown in Table IV. Where a mass was visible, the calcification was always found within the mass, as well as being present in the surrounding tissue in some cases (Fig. 3). This latter feature was clearly demonstrated in the stereoscopic projections.

In benign lesions there was a clinically palpable lump in only ten patients (Table III) and a mass was demonstrated radiologically in six of these. In four other cases without a definite clinical lump, mammograms revealed a mass in two and an area of disturbed architecture in two others. In the remaining 17 cases calcification was the only radiological abnormality. Where another radiological abnormality was present, the calcification was seen within the area of the abnormality in seven cases, and it was also deposited in the surrounding tissue in two other cases, but calcification was only in the surrounding tissue in one case (Table IV).

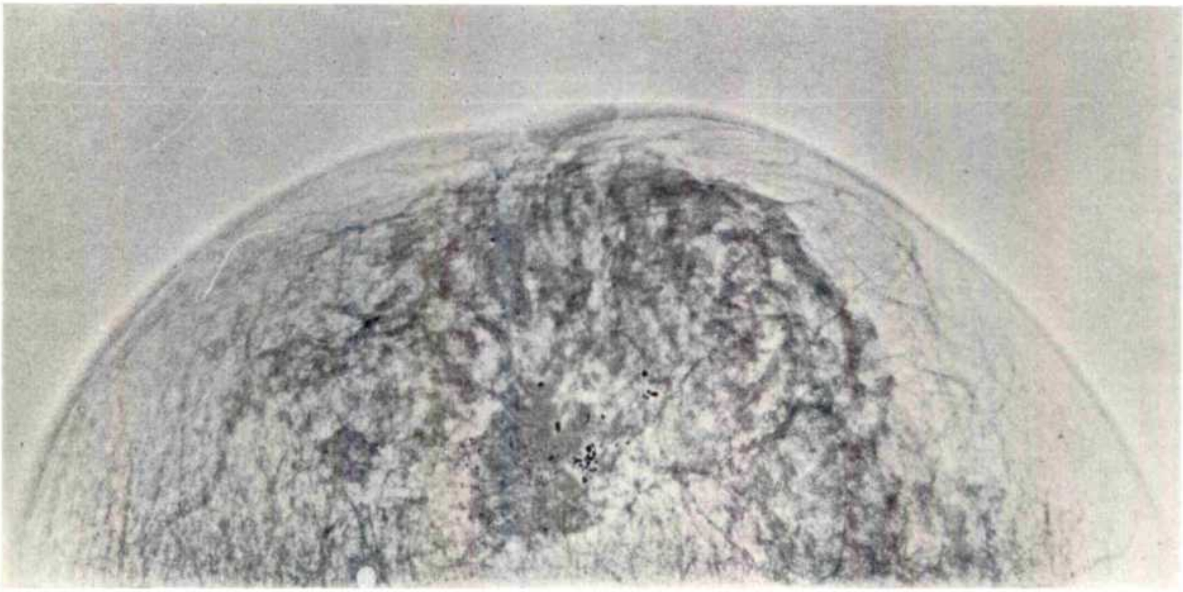


FIG. 3.

Obvious infiltrating carcinoma with calcification within the mass and surrounding tissue extending towards the nipple.

2. *Size of calcification*

The size of the particles of calcification is shown in Table V. Usually a range of sizes was found (Fig. 4), and the predominant size range was recorded. In those cases where the particles were more numerous, the range of size was wider. In both malignant and benign lesions particles varied from approximately 100 μm to 1,500 μm with an occasional larger particle. In only two carcinomas, both containing less than five calcifications, did all the particles measure over 1,000 μm across. One carcinoma contained a single 6×2 mm bilobed calcification; this patient had been treated with radiotherapy prior to mastectomy (Fig. 5).

3. *Number of calcifications*

The total number of calcifications seen within the area of the lesion is shown in Table VI. In only six carcinomas were there less than five particles, while in 16 the particles were too numerous to count.

In six cases of benign disease the particles were also very numerous, but usually there were fewer than commonly seen in association with carcinoma.

4. *Distribution of calcification*

The spatial distribution of the calcification on the mammograms is shown in Table VII and was sometimes difficult to classify. Localized clusters were no problem, but often although the particles were densely packed and often uncountable, they extended over a considerable area of the mammogram. In the carcinomas this usually occurred when there was widespread intraduct change either confined to the ducts or associated with infiltration. A not uncommon pattern consisted of a dense cluster of calcifications extending to the sub-areolar region. In two of the cases of carcinoma and two of the benign lesions the calcification was truly widespread; one of the carcinomas was multifocal and the other a case of *in-situ* lobular carcinoma with associated fibrocystic disease. Both the patients with benign

TABLE VI

NUMBER OF CALCIFICATIONS ON PRE-OPERATIVE MAMMOGRAMS OF PATIENTS WITH CARCINOMA AND BENIGN BREAST LESIONS

Number of calcifications	Carcinomas	Benign lesions
Less than 5 particles	6	5
5–9 particles	6	6
10–30 particles	5	10
Uncountable	16	6
Total	33	27

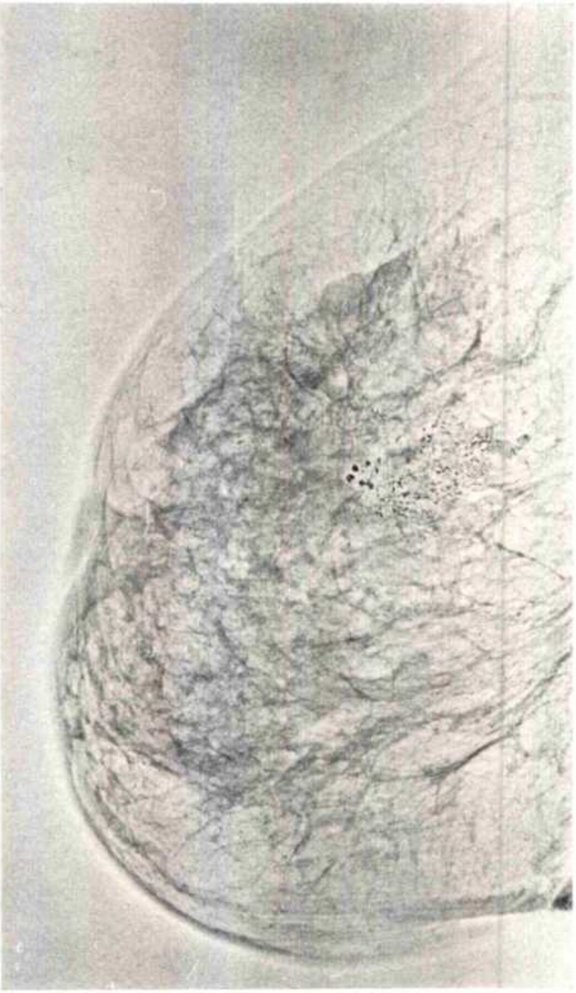


FIG. 4.

Infiltrating carcinoma of breast containing a large area of numerous clustered calcifications with a wide range of size and no obvious mass.

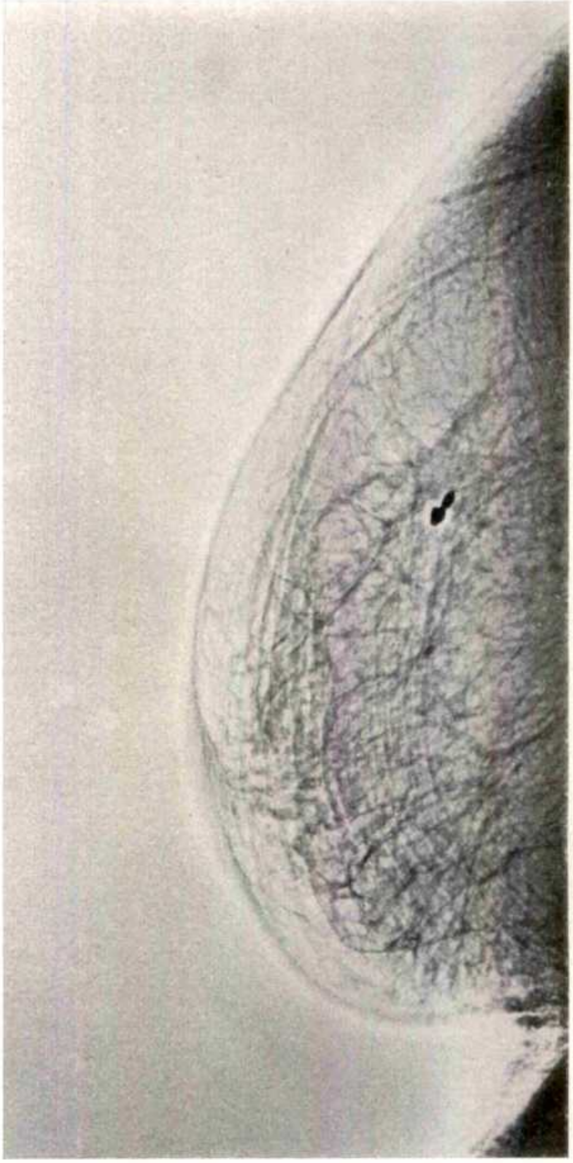


FIG. 5.

A single bilobed calcification occurring in a carcinoma treated with radiotherapy.

disease were thought to have carcinoma on clinical grounds. One elderly patient with a blood-stained nipple discharge had widespread duct papillomatosis and the other with contralateral *in-situ* lobular carcinoma had fibrocystic disease.

In patients with carcinoma and mammary dysplasia of the remaining breast, there were sparse widely scattered particles elsewhere on the mammogram, in addition to the calcification associated with the carcinoma.

Pathological features of carcinomas (both with and without calcification) and of benign breast lesions with calcification on pre-operative mammograms

1. *Type of carcinoma*

Tables VIII–XI give an analysis of the histological type of the carcinomas, the grade of the carcinomas (Bloom and Richardson, 1957), the pathological size of the tumours, and the number of involved lymph-nodes, comparing those with and without calcification on the pre-operative mammograms. The ten cases in which scant calcification was seen on histology, but not on mammography, are included with the carcinomas in which calcification was not found on mammograms. It will be seen that the two groups contain similar tumours.

The histology in the benign breasts showed a variety of disorders including fibroadenosis, cystic

TABLE VII

SPATIAL DISTRIBUTION OF CALCIFICATION ON PRE-OPERATIVE MAMMOGRAMS OF PATIENTS WITH CARCINOMA AND BENIGN BREAST LESIONS

Spatial distribution	Carcinoma	Benign
Closely packed over localized area	25	16
Closely packed over large area	5	6
Diffusely and evenly scattered throughout breast	2	2
Diffusely scattered throughout breast with one localized cluster	1	3
Total	33	27

TABLE VIII

HISTOLOGICAL TYPE OF ALL CARCINOMAS BOTH WITH AND WITHOUT CALCIFICATION ON PRE-OPERATIVE MAMMOGRAMS

Type of carcinoma	With* calcification	Without† calcification
Infiltrating duct carcinoma with associated *in-situ* duct change	18	24
In-situ intraduct carcinoma	8	3
Infiltrating tubular carcinoma	3	1
Infiltrating carcinoma with no *in-situ* change	1	5
Infiltrating carcinoma with *in-situ* lobular change	1	1
Mucoid carcinoma	1	0
Intracystic papillary carcinoma	0	1
In-situ lobular carcinoma	1	0
Total	33	35

*The two cases with calcification on pre-operative mammography and *not* on histology were both infiltrating carcinomas with intraduct change.

† The cases with calcification on histology but *not* on pre-operative mammograms consisted of six infiltrating carcinomas with intraduct change and four infiltrating carcinomas with no *in-situ* change.

TABLE IX

GRADE OF CARCINOMAS BOTH WITH AND WITHOUT CALCIFICATION ON PRE-OPERATIVE MAMMOGRAMS

Grade of carcinoma (Bloom and Richardson, 1957)	With calcification	Without calcification
Grade I	5	4
Grade II	13	18
Grade III	6	9
In situ carcinoma	9	4
Total	33	35

TABLE X

PATHOLOGICAL SIZE OF CARCINOMAS BOTH WITH AND WITHOUT CALCIFICATION ON PRE-OPERATIVE MAMMOGRAMS

Pathological size of tumour	With calcification	Without calcification
In situ	9	3
Infiltrating carcinoma up to 1 cm	2	5
Infiltrating carcinoma 1·1–2 cm	12	17
Infiltrating carcinoma 2·1–5 cm	10	10
Infiltrating carcinoma over 5 cm	0	0
Total	33	35

TABLE XI

NUMBER OF LYMPH-NODES CONTAINING METASTASES IN PATIENTS WITH AND WITHOUT CALCIFICATION ON PRE-OPERATIVE MAMMOGRAMS

Number of involved axillary lymph-nodes	With calcification	Without calcification
All nodes negative	11	15
One to five nodes involved	4	11
More than five nodes involved	7	2
Nodes not removed	11	7
Total	33	35

disease, sclerosing adenosis, pink cell metaplasia, duct ectasia, duct papillomatosis and epithelial hyperplasia.

2. *Histological site of calcification in carcinomas*

In nearly all cases the calcification was present within malignant tissue. In all cases of *in-situ* duct, and in most cases of infiltrating duct, carcinoma with *in-situ* change, calcification was present in the necrotic debris in the centre of the malignant ducts. These were frequently located around the edge of the main infiltrating tumour mass, thus giving the appearance on the mammogram of calcification outside the carcinoma (Fig. 3). In some cases, calcification was also found in benign ducts within and around the carcinoma as well as among the malignant cells and in a few cases (four) calcification was found only in benign ducts within and around the carcinoma. In the one mucoid carcinoma studied, calcification was seen within the mucoid stroma and in the irradiated carcinoma a large area of calcification similar in type to that often seen in fibroadenomas was present in the collagenous stroma. Large calcifications have since been seen in two more irradiated carcinomas.

3. *Histological site of calcification in benign breast lesions*

In benign breast disease, calcification was seen in the lumen of ducts and acini, in the wall of ectatic ducts, in areas of pink cell metaplasia, and in stroma.

4. *Histological size and appearance of calcification*

The individual particle size in both malignant and benign lesions ranged from less than 10 μm to 500 μm with aggregates of many particles measuring up to 1,500 μm. The microscopic appearances of the particles varied. The largest collections were seen within the necrotic material in the centre of malignant ducts (Fig. 6A and B) where the calcification appeared granular and was composed of numerous particles varying in size, usually irregular and angular in shape, but sometimes rounded or laminated. The overall texture of the calcification resembled that of the rather granular necrotic material in which it was deposited. This appearance was enhanced by the shattering of the calcium particles when sectioned. Frequently, calcification was seen only in the central portion of the necrotic material, but sometimes it was deposited around the periphery or was randomly distributed. This type of calcification was also seen in infiltrating areas of carcinoma and in benign tissue. However, in areas of infiltrating carcinoma both within tubules, among solid islands of malignant cells and within stroma, and in benign ducts and acini, the calcium particles were usually small, round, homogeneous or laminated, sometimes resembling psammoma bodies, occurring either singly, or in small groups (Fig. 7A and B). These latter calcifications sometimes appeared to be deposited within mucin present within the tissue. The calcification seen in areas of sclerosing adenosis nearly always consisted of small laminated particles (Fig. 8), but often larger round or irregular particles were seen in dilated benign ducts.

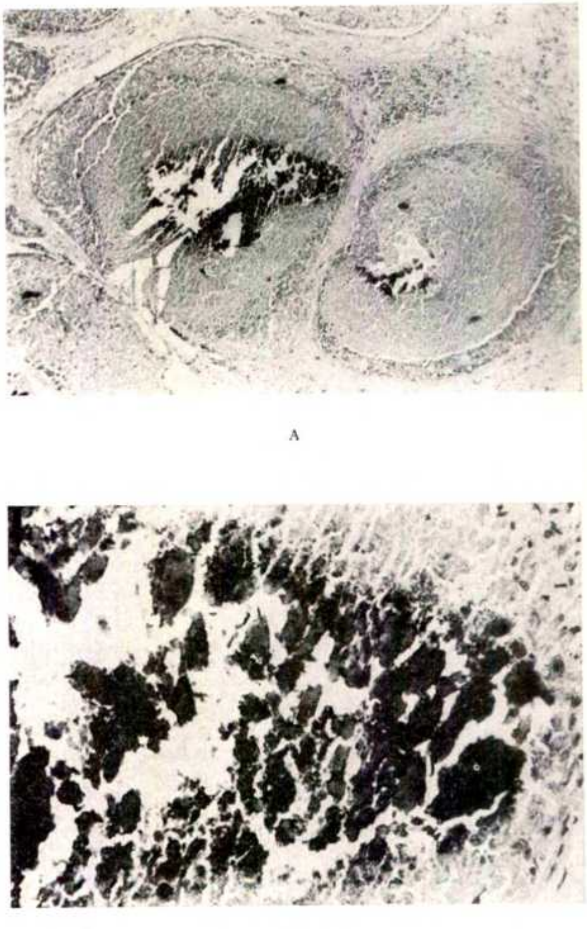


FIG. 6.

(A) Calcification in the centre of malignant ducts in an infiltrating and intraduct carcinoma. (Haematoxylin and eosin ×12·8.) (B) High-power view of the clusters of irregular calcification in the centre of the malignant ducts. (Haematoxylin and eosin ×80.)

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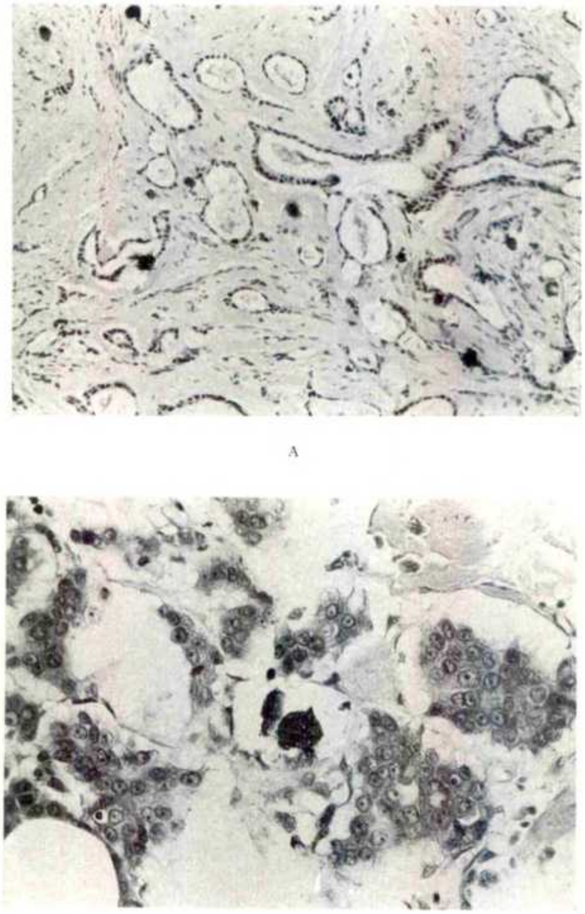


FIG. 7.

(A) Calcification in infiltrating carcinoma both within tubules and stroma. (Haematoxylin and eosin × 32.) (B) High-power view of rounded laminated calcification in an infiltrating carcinoma. (Haematoxylin and eosin × 128.)

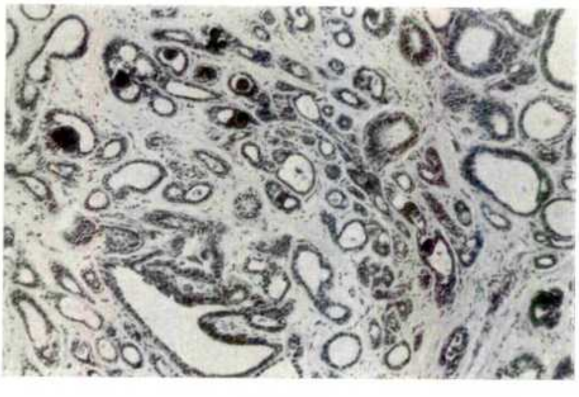


FIG. 8.

Calcification in sclerosing adenosis. (Haematoxylin and eosin × 32.)

DISCUSSION

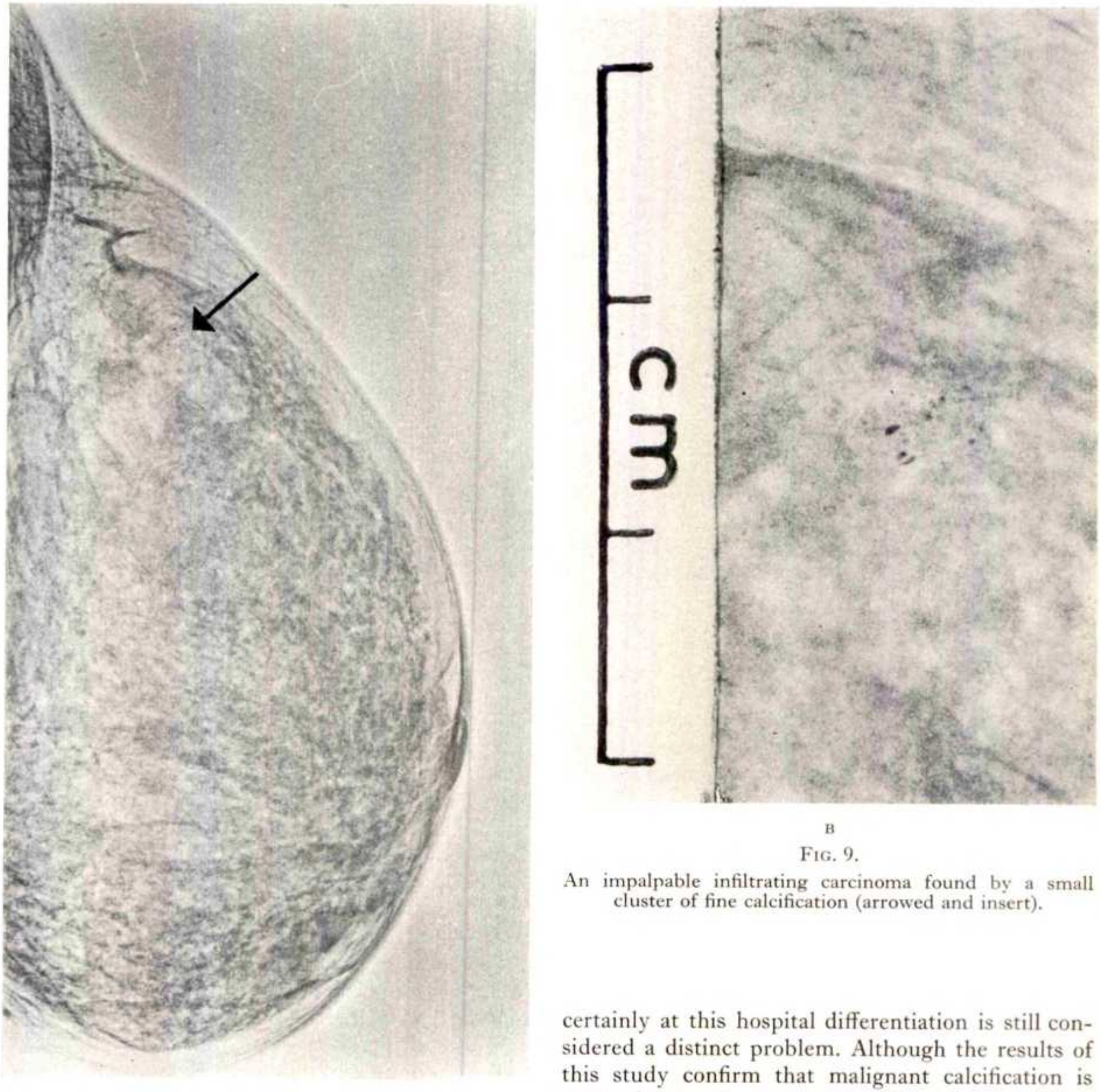
In the detection of fine calcifications it has been shown that xeroradiography has advantages over the conventional method, and, in many cases, provides additional radiological detail under the exposure conditions described. Although the quality of the PE 4006 and Medichrome films were found to be comparable to each other, the Medichrome film, used with an intensifying screen, has obvious advantages in sensitivity, whilst its specially designed viewing system affords a facility often neglected in radiology.

The deterioration of the image on film as the X-ray beam is hardened imposes restrictions on the conditions of use which are not experienced in xeroradiography.

In all of the techniques it was found that fine particles were more easily detected when they were located in groups of varying sizes; this would suggest that the presence of the larger particles provokes closer local scrutiny. No attempt has been made to illustrate the comparative appearance of calcification shown by the various recording media, as it will be appreciated that detail in conventional radiographs does not reproduce well and would be shown to disadvantage.

The importance of detecting fine particles is emphasized in the above study since 11 of the carcinomas contained predominantly fine calcification, and some fine particles were found in the majority of the other carcinomas (Table V). Benign lesions containing a wide range of particle size generally exhibited less fine calcification. However, the proportion of lesions containing predominantly fine calcification was similar in both malignant and benign breast disease. Since completing this work, several more carcinomas containing only fine calcification have been seen and in at least two of these cases, the tumour was detected solely by the presence of calcification on the mammogram in the absence of any clinical or other radiological abnormality (Fig. 9). The results in Part I of this report indicate that such cases may well be missed by mammography using film techniques.

When choosing a radiological technique, factors other than discrimination must of course be considered. Patient exposure is particularly important, and it is appreciated that conventional film techniques using an intensifying screen will result in a reduction in patient exposure when compared with xeroradiography. This rather complex subject is discussed in detail in another paper shortly to appear in this Journal.



A

B

FIG. 9.

An impalpable infiltrating carcinoma found by a small cluster of fine calcification (arrowed and insert).

The problem of establishing characteristic patterns of calcification in malignant and benign breast lesions has been the subject of several papers (Levitan *et al.*, 1964; Gershon-Cohen, Berger and Curcio, 1966; Wolfe, 1966; Egan, 1969; Minagi, 1969; Koehl *et al.*, 1970; Rogers and Powell, 1972). In the past most authors seem to have minimized the difficulty in distinguishing between the two. However, with increasing experience, there is a growing awareness that there is no definitive pattern that is pathognomonic of either condition, and certainly at this hospital differentiation is still considered a distinct problem. Although the results of this study confirm that malignant calcification is more frequently associated with a mass, more numerous and closely packed, and usually includes finer particles, none of these features are definitive and none can be taken in isolation. On many occasions malignant and benign lesions are indistinguishable, as illustrated in Figs. 2A and B and 10A and B. This agrees with the findings of Fisher, Dow and Posado (1973) who, after radiological examination of breast tissue slices containing malignant and benign lesions, concluded "that there is no distinctive pattern of calcification which *per se* is pathognomonic of mammary carcinoma".

The radiological density and shape of the particles of calcification is not recorded in this study as these

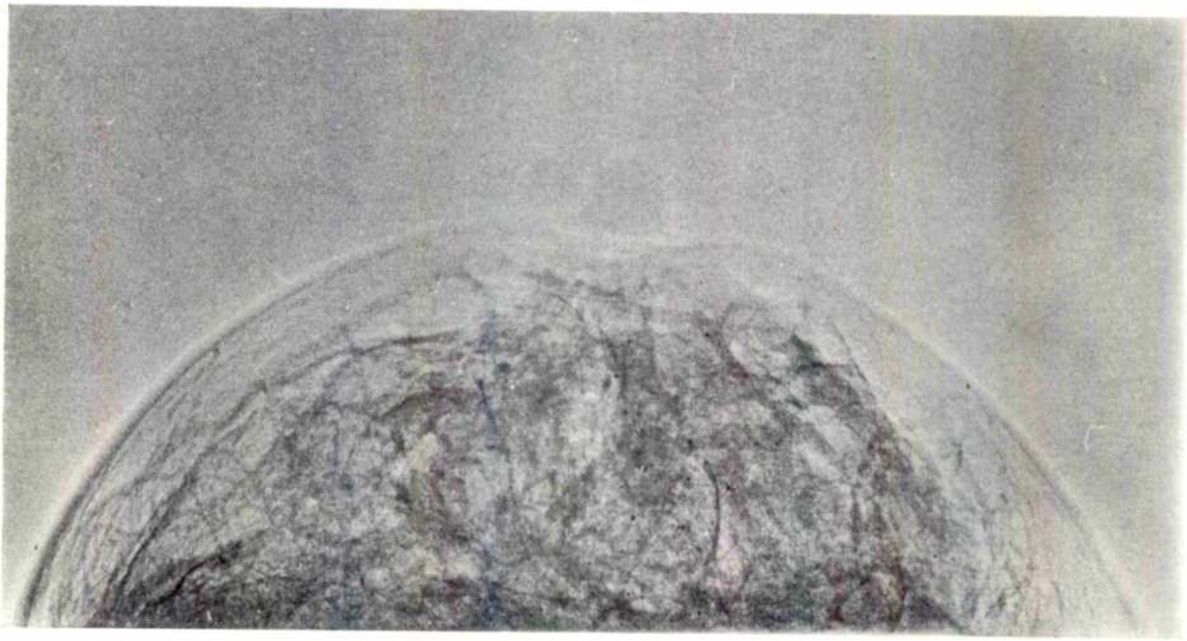


FIG. 10A.
Fairly widespread calcification in a case of infiltrating carcinoma with *in-situ* intraduct change.

features have not been found helpful in distinguishing between malignant and benign lesions (apart from the obvious coarse "benign" calcifications of a fibroadenoma or duct ectasia). It was also found impractical to determine the shape of fine particles.

Reports on the incidence of calcification in carcinoma of the breast in pre-operative mammograms using conventional film, range from approximately 30–40 per cent. When tissue blocks or slices of specimens are examined, higher percentages are reported, usually ranging from approximately 40 to 60 per cent (Leborgne, 1953; Shepherd, Crile and Strittmatter, 1962; Levitan *et al.*, 1964; Black and Young, 1965; Gershon-Cohen *et al.*, 1966; Egan, 1969; Koehl *et al.*, 1970; Rosen, Snyder, Foote and Wallace, 1970), although an incidence as high as 86 per cent has been found by one group of workers (Fisher *et al.*, 1974). Calcification was demonstrated on pre-operative mammography in 48·5 per cent of patients with carcinoma in this study. This slightly higher incidence may largely be accounted for by the easier visualization of fine particles by xeroradiography.

There were, however, some cases in which occasional small calcifications seen on histology, were not demonstrated on the pre-operative mammogram. For the purposes of this study, these were grouped with the cases in which calcification was not seen either on radiology or histology since it is considered that multiple sections of any carcinoma may well reveal many more small foci of calcification. Such small particles can be detected on the pre-operative mammogram only when they are more numerous and close together. Radiological examination of surgical specimens of breast lesions did not reveal significant additional amounts of calcification in this study in contrast to the findings of other workers using conventional film (Bauermeister and Hall, 1973; Egan, 1969; Rosen *et al.*, 1970). This is consistent with the results in Part I which showed that fine calcification within mastectomy specimen and in phantoms is more easily demonstrated by xeroradiography.

There are few reports on the incidence of calcification in benign breast disease in pre-operative mammograms. An incidence of 23 per cent has been reported (Rosen *et al.*, 1970; Koehl *et al.*, 1970) based on *specimen radiography* using film. The 20 per cent incidence in this series seen on *pre-operative mammograms* compares extremely favourably with this figure.

The histological size of the majority of the calcifications appeared smaller than the radiological size. To clarify this, selected thin 0·5 cm slices of breast tissue containing many calcifications of various sizes were cleared with xylene and the calcifications

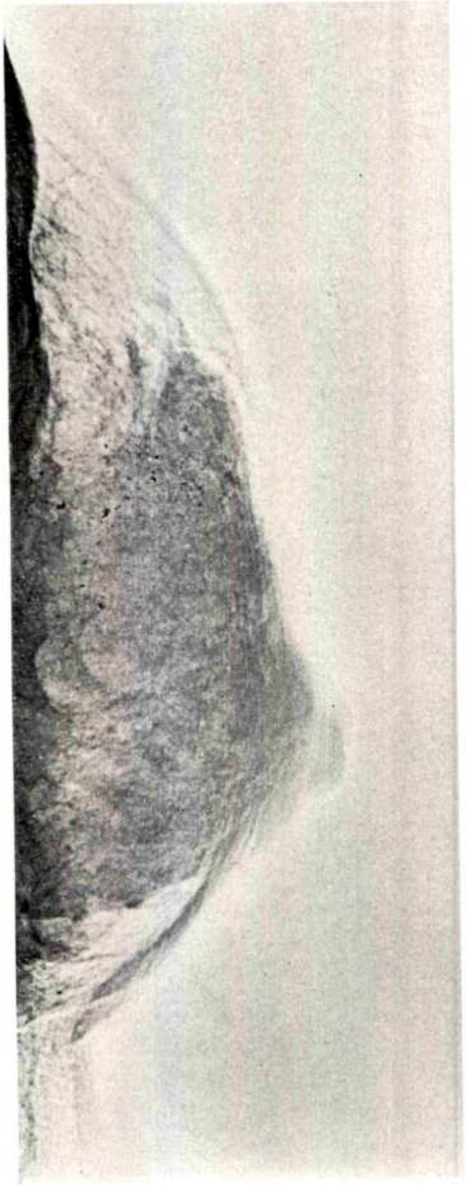


FIG. 10B.

Similar widespread calcification in benign breast disease (fibrocystic disease).

stained using alazarin red. The calcifications in the cleared tissue were then measured microscopically, photographed, radiographed within a fat-equivalent phantom using both film and xeroradiography, and the specimen finally processed histologically. The particles were measured on each occasion. This showed that the discrepancy in size was due to a number of factors including:

(1) the edge effect of xeroradiography;

(2) the irregular shape of the calcifications which are only occasionally sectioned across their greatest diameter;

(3) the fact that several small particles in close proximity appear as a single calcification radiologically.

This technique using cleared specimens has also proved valuable in some of the subsequent work, which includes the evaluation of image quality under other film-screen combinations, and the investigation of the effect of exposure parameters (including patient movement) on the apparent radiological density and shape of particles.

The histological site and appearance of calcifications described above is similar to findings by other workers (Levitan *et al.*, 1964; Patton *et al.*, 1966; Gershon-Cohen *et al.*, 1966; Hassler, 1969; Koehl *et al.*, 1970). However, although the appearances of the particles varied, no one type was peculiar to either malignant or benign lesions.

The appearance of the calcification is possibly determined by the nature of the tissue in which it is deposited rather than the histological type of the surrounding cells. The irregular calcification typically seen in the centre of malignant ducts seems to be deposited in degenerating and necrotic cells. The round or laminated particles usually seen amongst infiltrating tumours or in benign ducts are often deposited among mucinous secretions. When located in the stroma, the calcification has presumably remained trapped after the original surrounding epithelial cells have degenerated and disappeared. Comparison of carcinomas containing calcification and those in which calcification was not demonstrated in pre-operative mammography shows that the tumours are similar in respect of their histological type, grade (Bloom and Richardson, 1957), pathological size and the number of involved axillary lymph-nodes.

CONCLUSIONS

Smaller particles of calcification have been detected within breast tissue using xeroradiography than were demonstrated using conventional film techniques. Visualization of all fine calcification is enhanced by the use of this technique. These advantages may be attributed to the "edge effect" combined with the wide exposure latitude of the xeroradiographic process. This technique may also be used with radiation beams of harder quality which are generally considered unacceptable for use with film techniques.

Calcifications of varying size are found in many carcinomas. The detection of fine particles is particularly important when they are the only indication of an occult carcinoma. No definitive features are found distinguishing between calcification occurring in malignant and benign breast lesions. No difference is found in the pathology of carcinomas containing calcification and those without calcification. The incidence of calcification recorded on the pre-operative mammograms in cases of carcinoma of the breast in this series is 48·5 per cent. This relatively high incidence is attributed to the easier visualization of fine particles using xeroradiography.

Acknowledgments

This project would not have been possible without the co-operation and advice of many of our colleagues in various departments of the Royal Marsden Hospital and the Institute of Cancer Research. We would first like to thank Dr. Iris M. E. Hamlin (Consultant Pathologist) for her continued interest and useful discussion. Encouragement and advice was also received from Professor J. W. Boag, Director of the Division of Physics. Our thanks are further extended to Mr. W. P. Greening and Mr. J. A. McKinna (Breast Unit and Department of Surgery), Dr. J. J. Stevenson, Dr. K. A. Tonge (Department of Diagnostic Radiology), the staff of the Diagnostic Radiology Department and the histopathology technicians for their help. It is a pleasure to record our debt to Miss Ann V. Casey of the Ravenor Park Clinic for assistance with the use of the Medichrome film. Finally we gratefully acknowledge both the Medical Art and Photographic Departments for assistance with the diagram and figures in the text. One of the authors, Dr. R. Millis, is a research assistant on a grant from the Eranda Trust of the Breast Unit, Royal Marsden Hospital.

REFERENCES

Bauermeister, D. E., and Hall McLure, H., 1973. Specimen radiography—a mandatory adjunct to mammography. *American Journal of Clinical Pathology, 59,* 782–783.

Black, J. W., and Young, B., 1965. A radiological and pathological study of the incidence of calcification in diseases of the breast and neoplasms of other tissues. *The British Journal of Radiology, 38,* 596–598.

Bloom, H. J. G., and Richardson, W. W., 1957. Histological grading and prognosis in breast cancer. *British Journal of Cancer, 11,* 359–377.

Boag, J. W., Stacey, A. J., and Davis, R., 1971. Some clinical and experimental applications of xeroradiography. *Journal of Photographic Science, 19,* 45–48.

1972. Xeroradiographic recording of mammograms. *British Journal of Radiology, 45,* 633–640.

Egan, R. L., 1969. Fundamentals of mammographic diagnosis of benign and malignant diseases. *Oncology, 23,* 126–148.

1972. *Mammography,* 2nd ed. (Thomas, Chicago).

Fisher, E. R., Dow, W. A., and Posada, H., 1973. Correlations between specimen roentgenograms (mammograms) and pathologic findings in breast disease. In *Pathology Annual,* edited by Sheldon C. Somers, pp. 453–472 (Appleton-Century-Crofts, New York).

Fisher, E. R., Posada, H., and Ramos, H., 1974. Evaluation of mammography based upon correlation of specimen mammograms and histopathologic findings. *The American Journal of Clinical Pathology, 62,* 60–72.

Gillbe, P., 1973. Xeroradiography of the breast. *Radiography 39,* 127–135.

Gershon-Cohen, J., Yui, Lorna S., and Berger, S. M., 1962. The diagnostic importance of calcereous patterns in roentgenography of breast cancer. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 88,* 1117–1125.

Gershon-Cohen, J., Berger, S. M., and Curcio, B. M. 1966. Breast cancer with microcalcifications: Diagnostic difficulties. *Radiology 87,* 613–622.

Hassler, O., 1969. Microradiographic investigations of calcifications of the female breast. *Cancer, 23,* 1103–1109.

Koehl, R. H., Snyder, Ruth E., Hutter, R. P., and Foote, F. W., 1970. The incidence and significance of calcifications within operative breast specimens. *The American Journal of Clinical Pathology, 53,* 3–14.

Leborgne, R., 1949. Diagnostico de los tumores de la mama por la radiographia simple. *Boletin de la Sociedad de Cirurgia de Uruguay, 20,* 407–422.

1953. *The Breast in roentgen diagnosis.* pp. 124 (Impresora Uruguaya S.A., Montevideo, Uruguay,).

Levitan, L. H., Witten, D. M., and Harrison, E. G., 1964. Calcification in breast disease, mammographic—pathologic correlation. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 92,* 29–39.

Minagi, H. 1969. Sources of error in mammography. *Oncology, 23,* 164–166.

Patton, R. B., Poznanski, A. K., and Zylack, C. J., 1966. Pathologic examination of specimens containing non-palpable breast cancers discovered by radiography. *American Journal of Clinical Pathology, 46,* 330–334.

Rogers, J. V., and Powell, R. W., 1972. Mammographic indications for biopsy of clinically normal breasts: correlation with pathological findings in 72 cases. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 115,* 794–800.

Rosen, P., Snyder, Ruth E., Foote, F. W., and Wallace, Thelma, 1970. Detection of occult carcinoma in the apparently benign breast biopsy through specimen radiography. *Cancer, 26,* 944–952.

Shepherd, T. J. Crile, G., and Strittmatter, W. C., 1962. Roentgenographic evaluation of calcifications seen in paraffin block specimens of mammary tumours. *Radiology, 78,* 967–969.

Wolfe, J. N., 1966. Mammography: errors in diagnosis. *Radiology, 87,* 214–219.

Xeroradiography of the Breast (Charles C. Thomas, Springfield, Illinois).

1976, *British Journal of Radiology*, *49*, 27–33

Congenital aganglionosis of the entire colon in neonates

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(*Received June, 1975*)

ABSTRACT

A report of six cases and their radiological diagnosis in neonates. Total colonic aganglionosis (TCA) is a variety of what is commonly known as long segment Hirschsprung's disease. This is not a rare condition, but is often unrecognized. It has a high mortality, frequently with a complicating enterocolitis. Aganglionosis of some part of the colon should be suspected in all babies who show obstructive plain film changes. In TCA the barium enema changes may easily be passed as unremarkable. However, free ileal reflux during the examination, with a transition point in the ileum, and retention of barium in the entire colon after the examination, are diagnostic.

The term Hirschsprung's disease cannot correctly be applied to total colonic aganglionosis, as the original description implied a megacolon, and therefore only correctly applies to aganglionosis involving the distal colon (Ehrenpreis, 1970). The absence of a dilated proximal colon makes diagnosis difficult, leads to delay in treatment, and to high neonatal mortality. We do not agree with Sane and Girdany (1973) that radiographic findings are not diagnostic. Previous reports of barium enema diagnosis have been made by Berdon, Koontz and Baker (1964), Frech (1968), Chandler and Zwiren (1970) and Deffrenne, Daudet and Chappuis (1971).

Congenital aganglionosis is a common cause for intestinal obstruction in the young infant. In a six-year period (1969–74) at the Red Cross Children's Hospital, Cape Town, 80 per cent of the cases of this condition presented in the neonatal period, an average of twelve per year (Cremin, 1974). The great majority were of the "short segment" type, length 5–25 cm, and involving only the rectosigmoid colon. There was an average of two cases per year of the "long" segment variety, in which the colon proximal to the rectosigmoid junction was involved. In the latter group, six patients were seen during the six-year period in whom at least the entire colon was involved and details of these cases follow.

CASE REPORTS

Case 1

This female infant, who was born normally at term, was admitted in a dehydrated state at six days of age because of bilious vomiting and bloody diarrhoea for three days.

Radiological features

The plain radiograph of the abdomen showed evidence of dilation of the small bowel with multiple fluid levels. The inverted lateral radiograph showed no gas in the rectum. Hirschsprung's disease was suspected, and a careful barium enema done. The barium flowed without obstruction to the caecum with free reflux into the terminal ileum, a high degree of incompetency of the ileo-caecal valve being noted during the examination. The injection of the barium was discontinued immediately and it was noted that the distal 4 cm of the terminal ileum were extremely narrow (Fig. 1). Proximal to this, the ileum was dilated and the transition zone between narrowed and dilated segments was gradual, being approximately 3 cm in length. The whole of the colon had an abnormal appearance (Fig. 2); the walls were shaggy and irregular in outline. Deep indentations of the wall were present, representing an abnormal and inefficient contractile pattern. The colon was normally situated, but lacked the redundancy usually seen in the rectosigmoid region. The 24-hour radiograph (Fig. 3) showed some retention of barium throughout the colon, despite the presence of enterocolitis.

The diagnosis of total colonic aganglionosis was made and an ileostomy performed. After correction of the dehydration and improvement of the child's general condition, multiple biopsies were taken, which confirmed the extent of the aganglionosis. The child has improved clinically with no further surgery to date (six months).

Case 2

This male infant was admitted aged one month after a normal full-term delivery. The baby had diarrhoea and vomiting for one week prior to admission, and had been treated for gastro-enteritis. Preliminary examination revealed a distended abdomen in a slightly dehydrated infant.

Radiological features

Plain radiographs of the abdomen showed dilated loops of small bowel with fluid levels, and the inverted lateral

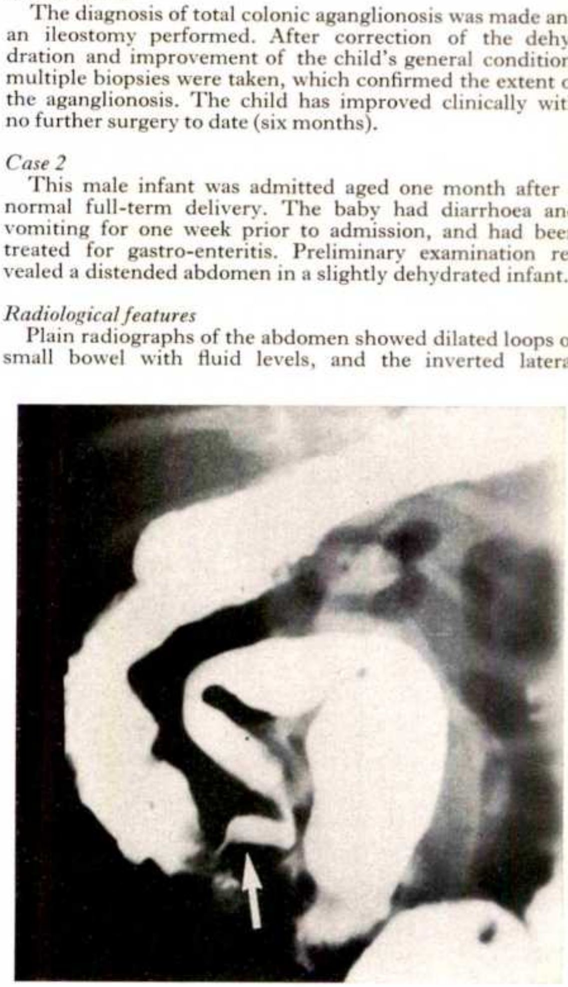

FIG. 1. *Case 1.*

Barium enema showing reflux into narrowed terminal ileum (arrow) which dilates into a transition zone.

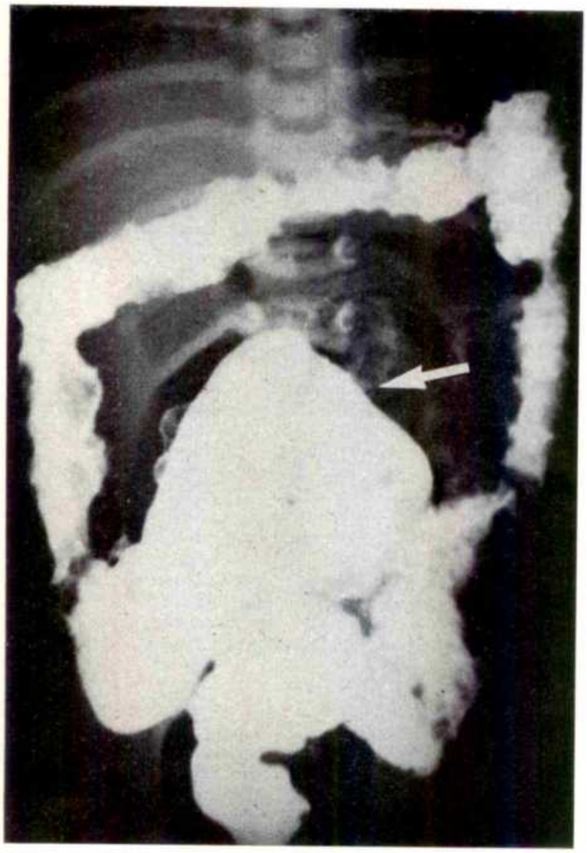

FIG. 2. *Case 1.*
Barium enema showing irregular colon from enterocolitis and free reflux into dilated ileum (arrow).

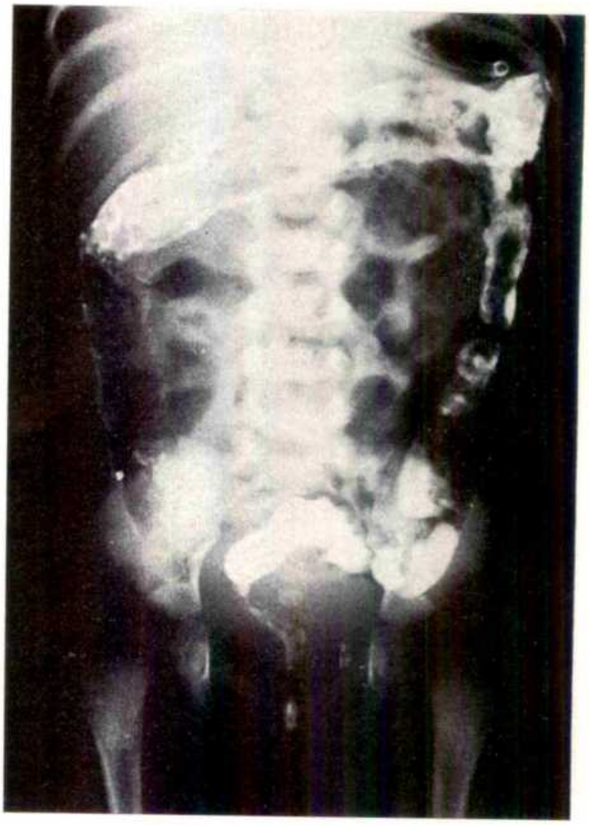

FIG. 3. *Case 1.*
Twenty-four hour delayed radiograph showing foreshortened colon and limited retention of barium due to the presence of enterocolitis.

radiograph showed an "egg on end" appearance, with no gas present in the rectum (Fig. 4). An inexperienced examiner reported on the barium enema as normal; the lack of redundancy of the rectosigmoid and splenic flexures, the slightly rippled contour and the immediate reflux into the dilated terminal ileum were not appreciated (Fig. 5). Our normal procedure of a 12-hour film was not followed and a further radiograph of the abdomen was not taken until six days later (Fig. 6). This showed dilated loops of small bowel and complete retention of barium in a colon that lacked redundant flexures. A diagnosis of total colonic aganglionosis was made and confirmed by multiple biopsies. Unfortunately the child had an intragastric bleed and died the following day. At autopsy, total colonic aganglionosis was again confirmed and in addition there was a perforated duodenal ulcer with associated generalized peritonitis and bilateral bronchopneumonia.

Case 3

This was a 23-day-old female infant who developed diarrhoea and vomiting at the age of three weeks. The symptoms persisted, and the continued vomiting led to a barium enema at another hospital.

Radiological features

The colon was reported to have had a markedly irregular border with irregular areas of peristalsis. This was interpreted as colitis. A radiograph taken 12 hours later (Fig. 7) showed retention of barium in the colon which had a markedly irregular contour with many fine rippled areas. The small bowel showed obstructive features. On the basis of these appearances, a diagnosis of colitis complicating a total aganglionosis of the colon was suggested. The diagnosis was proved at biopsy but the child has been lost to follow-up.

Case 4

This male infant (two weeks post mature) was admitted at 24 hours of age, having passed meconium, but suffering from bilious vomiting and abdominal distension.

Radiological features

Plain radiograph of the abdomen showed dilated loops of small bowel. The colon contained some gas, and bubbly meconium was present on the right side. Abdominal distension became gross and a nasogastric tube was passed into the stomach for drainage, and produced bile-stained fluid. At this stage a surgical obstruction was considered and a barium enema (Fig. 8) was done. This showed the presence of enterocolitis, with a shaggy colonic border and deep indentations and an oedematous cobblestone mucosa. There was free reflux into the terminal ileum which was of narrow calibre for its distal five loops, but proximal to that it was dilated. The 24-hour radiograph showed retention of only a small amount of barium. At this stage the child had developed diarrhoea. In this case the transition point in the ileum was correctly identified and the diagnosis arrived at,

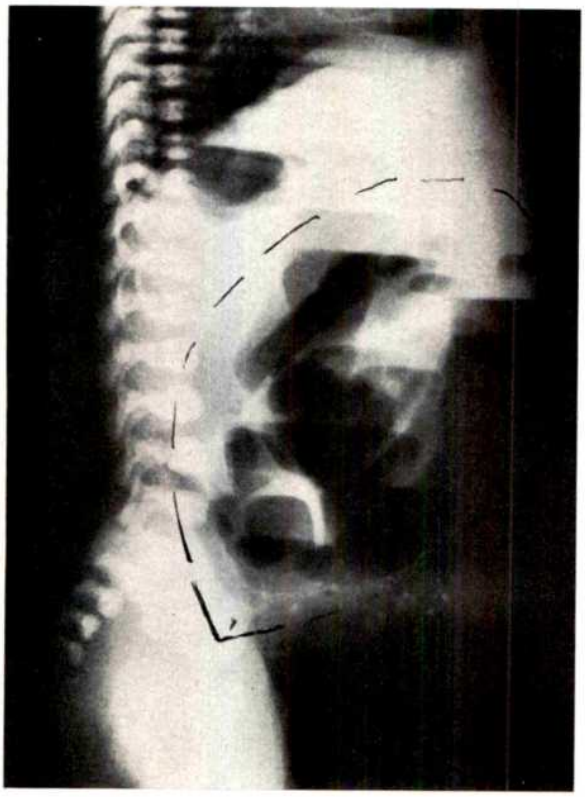

FIG. 4. *Case 2.*

Inverted lateral radiograph showing a lack of gas in the rectum and "egg on end" appearance. The apex of the egg points to the pelvis.

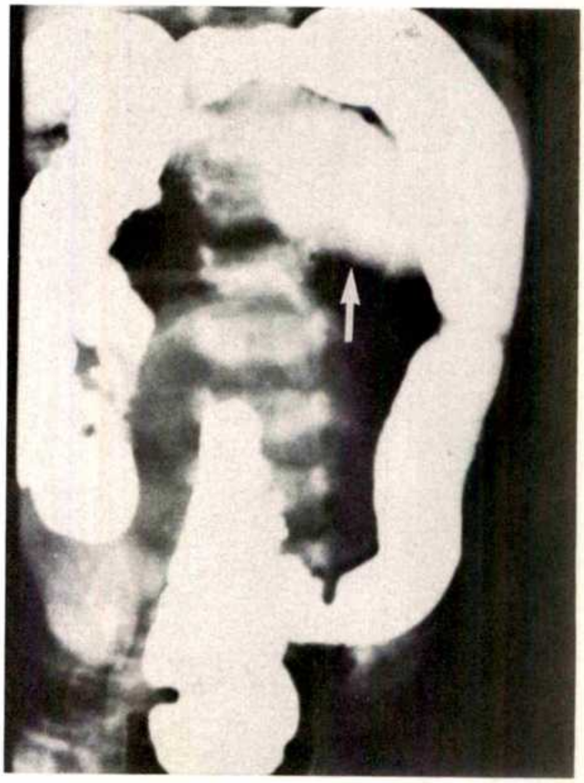

FIG. 5. *Case 2.*

Barium enema showing free reflux into dilated ileum (arrow).

but unfortunately the baby died some hours after examination. Autopsy showed the presence of enterocolitis and TCA with involvement of the terminal ileum as well.

Case 5

This baby girl was transferred from another hospital at three weeks of age. She had had persistent bilious vomiting since birth.

Radiological features

A barium enema had been performed three days previously, and no abnormal features were reported, but there was free reflux into the terminal ileum. A radiograph taken on admission to our hospital showed small bowel obstruction and barium retained in a small contracted colon (Fig. 9). Multiple biopsies showed aganglionosis of the entire colon but despite an ileostomy, the child died from generalized sepsis. Post-mortem examination showed aganglionosis of the colon and the whole of the ileum.

Case 6

This female infant, who had a normal full-term birth seven days previous to admission, had passed meconium stools, but had suffered from abdominal distension and recurrent bile-stained vomiting. A sibling had died in the neonatal period from vomiting of unknown cause.

Radiological features

The plain radiographs showed obstructive fluid levels and the inverted lateral film showed a small amount of rectal air, but none of the full rectal distension normally seen on taking an inverted film. The barium enema examination was performed in December, 1974, and was unremarkable except for immediate ileal reflux (Fig. 10). Proximal to this there were dilated gas-filled ileal loops. The "delayed" films at 12 hours showed barium retention, but the small amount of barium previously noted in the terminal ileum had now diffused widely throughout ileum (Fig. 11). A film taken at 48 hours showed the same barium retention with some shortening of the colon. TCA was suspected and a laparotomy was performed. Ganglion cells were absent from biopsies of the descending and left transverse colon, but in the small specimen obtained from the hepatic flexure, the aganglionosis was equivocal, so that right transverse colostomy was performed. The infant continued to suffer from alternating periods of diarrhoea and constipation associated with vomiting and abdominal distension. At four months of age the plain radiographs showed gross small bowel distension, and the infant was re-admitted to the surgical wards. At surgery, the small bowel was markedly distended up to the ileal-caecal valve, and further biopsies of the remaining segment of colon now established the diagnosis of total colonic aganglionosis.

DISCUSSION

TCA is probably more unrecognized than rare, and our experience confirms the findings of Frech

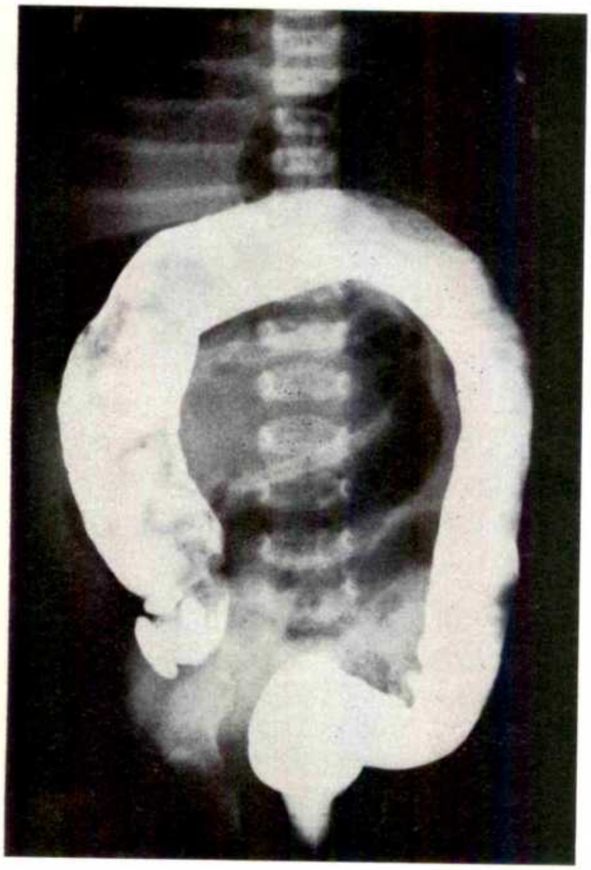

FIG. 6. *Case 2.*
Six-day film after barium enema showing retention of barium in a foreshortened colon with dilated gas-filled small bowel.

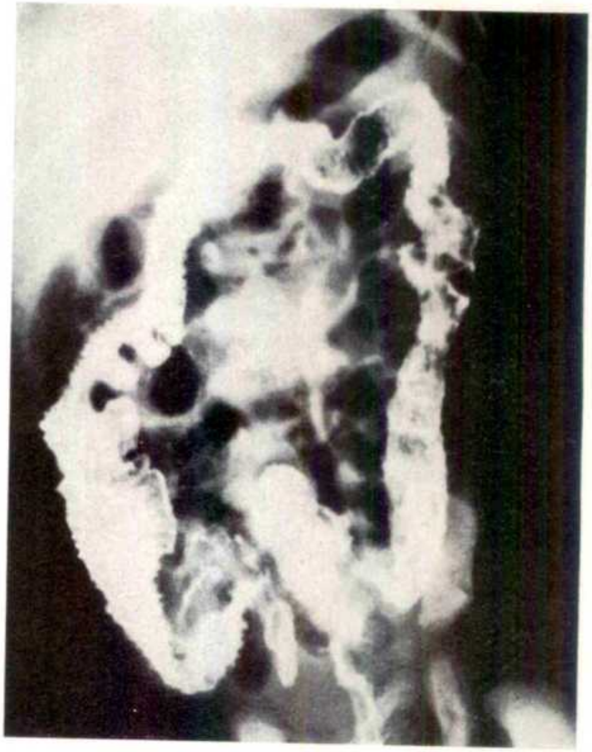

FIG. 7. *Case 3.*
Twelve-hour film showing retention of barium and irregularities consistent with enterocolitis.

(1968) that total aganglionosis can be expected about once a year in a paediatric hospital. The sex incidence in TCA is more evenly distributed than the 3:1, male : female ratio of the short segment variety (Edelman *et al.*, 1960). We suspect Hirschsprung's disease in all infants with a history of intermittent vomiting and diarrhoea who have multiple fluid levels on the plain radiograph. An inverted lateral radiograph that shows a deficiency of rectal gas and dilated small bowel giving an "egg on end" appearence (Deffrenne *et al.*, 1971; Cremin, 1974) is a reliable finding in this condition; all these cases have a barium enema. TCA is suspected when the following features are noted:

1. The colon fills relatively easily, and there may be no particularly abnormal features on fluoroscopy.
2. The colon frequently has a shaggy irregular contour or marked areas of abnormal rippling. These changes may be due either to enterocolitis or to irregular and non-effective colonic contractions.
3. Free and rapid reflux occurs into the terminal ileum even when no particular effort is made to fill this portion of bowel. If the aganglionosis terminates in the terminal ileum, then a transition zone and proximal dilatation may be noted in the terminal ileum.
4. There is a disparity between the size of the colon and of the small bowel resulting in a mega-ileum which contrasts with the relatively narrowed colon.
5. Retention of barium occurs in the whole colon, the amount depending on the presence or not of enterocolitis.
6. A loss of the natural redundancy of the flexures of the infant's colon may result in a shortened

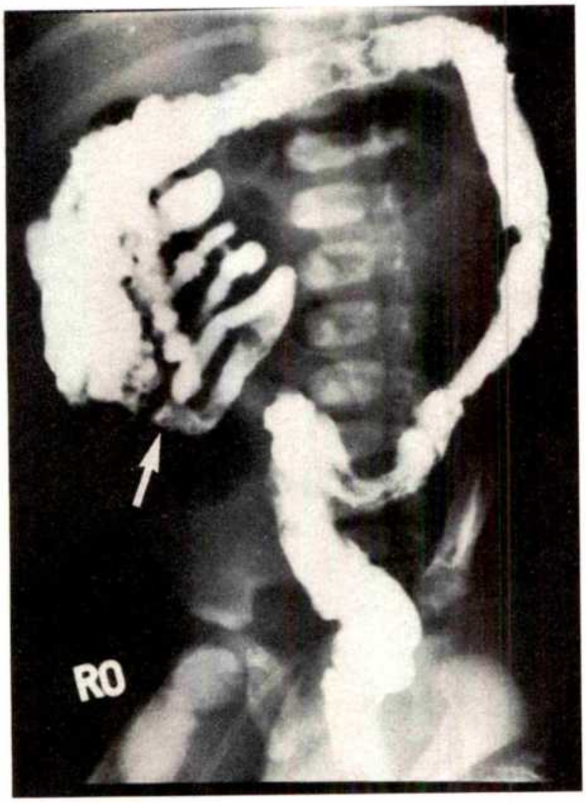

FIG. 8. *Case 4.*
Barium enema showing foreshortened colon and free reflux into narrowed aganglionic ileum (arrow) and proximal dilatation of gas-filled bowel.

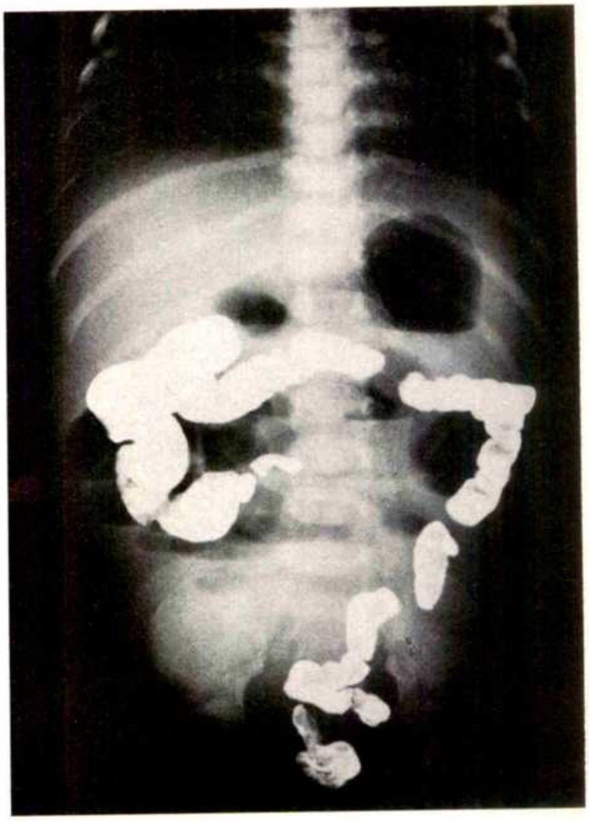

FIG. 9. *Case 5.*
Radiograph taken three days after barium enema showing retention of barium in a foreshortened colon, with small bowel obstruction.

appearance. This is best seen in the delayed radiographs when the relatively contracted state has re-asserted itself. This is a feature that is easily overlooked or not apparent at fluoroscopy during the filling stage of the enema.

These points need further elaboration. When gross obstructive features are seen in the plain abdominal radiograph, colonic aganglionosis, either partial or total, should be suspected. A barium enema must be done before rectal washouts are given to relieve the obstruction.

Free and unprovoked ileal reflux occurred in all barium enemas done in the department, and was the single, most informative feature of the examination. When it occurs in suspected cases the enema should be terminated as reflux into the stomach with aspiration pneumonia has been reported (Castellino *et al.*, 1968; Chandler and Zwiren, 1970). The aganglionic colon is incapable of normal peristalsis, so that contractions are liable to propel barium in a retrograde direction up the small bowel (Hiatt, 1951). Total colonic aganglionosis is an incomplete term, as it may imply that the condition is limited to the colon, whereas in the majority of cases the small bowel at least in its terminal portion is involved.

Enterocolitis is a common complication; it affected the whole colon in three of our six cases. The aetiology is uncertain, but an underlying vascular abnormality is possible, the autonomic nervous system controlling the tone of the vessels being impaired in the same way as is the peristaltic activity.

The foreshortening of the colon, particularly at the flexures, has been stressed by previous authors (Berdon, Koontz and Baker, 1964; Frech, 1968; Chandler and Zwiren, 1970; Deffrenne, Daudet and Chappuis, 1971). This is an extremely difficult sign

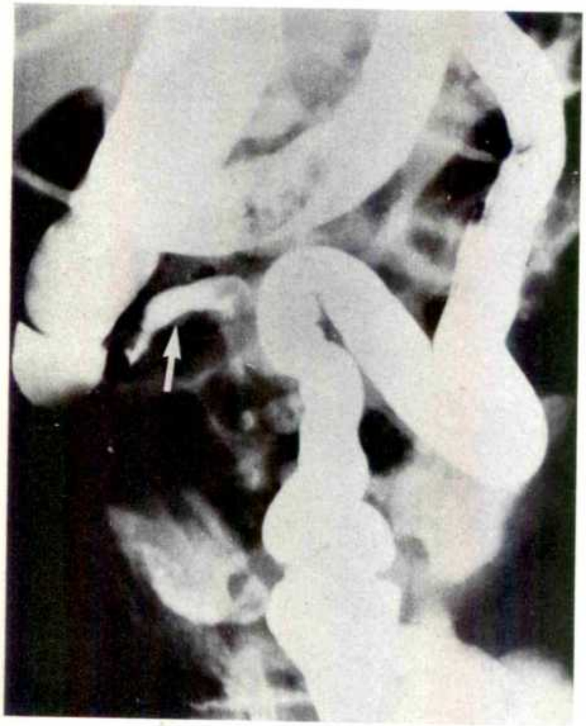

FIG. 10. *Case 6.*
Barium enema showing reflux into a narrow terminal ileum (arrow) and small bowel obstruction proximal to this

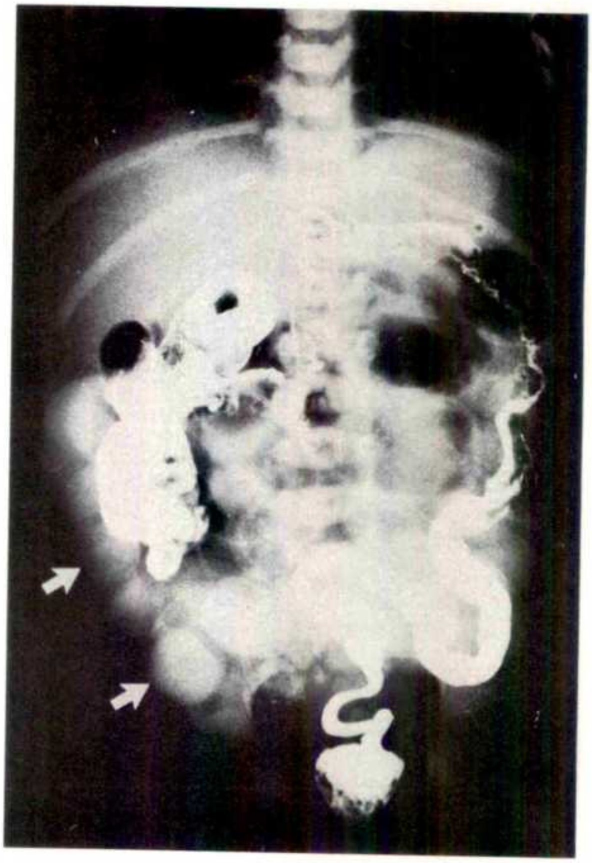

FIG. 11. *Case 6.*
Twelve-hour radiograph showing retention of barium in colon. There is diffuse opacification of the dilated small bowel from reflux (arrows).

to evaluate, and requires extensive experience in the appearance of the normal neonatal colon. The delayed radiographs (Cremin, 1971; Cremin, Cywes and Louw, 1973; Cremin, 1974) best demonstrate this appearance and are invaluable to show the retention of barium. Unless immediate surgery has to be performed, the examination is not complete without them.

TCA has been reported in later childhood (Stone, Hendrix and Schuster, 1965; Gerald, 1965), but the great majority of cases are seen as acute emergencies in the neonatal period. When a barium enema in an obstructed infant features the diagnostic points set out in this paper, laparotomy with frozen section biopsies of the whole colon is advised. Only in this manner may a prompt and life-saving ileostomy be indicated.

ADDENDUM

Since submitting the article for publication, we have had a further proved case of total colonic aganglionosis, also involving a fairly long segment of the terminal ileum.

The contrast enema revealed the presence of large meconiun plugs in an otherwise normal-appearing colon. The small intestine was dilated. Reflux into the terminal ileum did not occur, possibly because of plugs in the caecum.

The association of meconium plugs with total colonic aganglionosis has been described (Frech, 1968), but this is the only case in our experience to show this association to date.

ACKNOWLEDGMENT

Acknowledgment is made to Butterworths for the use of Fig. 9, from *Radiological Diagnosis of Digestive Tract Disorders in the Newborn: A guide to Radiologists, Surgeons and Paediatricians.*

REFERENCES

BERDON, W. E., KOONTZ, P., and BAKER, D. H., 1964. The diagnosis of colonic and terminal ileal aganglionosis. *American Journal of Roentgenology*, *91*, 680–689.

Castellino, R. A., Verby, H. D., Friedland, G. W., and Northway, W. H., Jr., 1968. Delayed barium aspiration following complete reflux small bowel enema. *British Journal of Radiology*, *41*, 937–939.

Chandler, N. W., and Zwiren, G. T., 1970. Complete reflux of the small bowel in total colon Hirschsprung's disease. *Radiology*, *94*, 335–339.

Cremin, B. J., 1971. The delayed film in Hirschsprung's disease. *South African Medical Journal*, *45*, 67–69.

Cremin, B. J., Cywes, S., and Louw, J. H., 1973. *Radiological Diagnosis of Digestive Tract Disorders in the Newborn. A guide to Radiologists, Surgeons and Paediatricians* (Butterworths, London).

Cremin, B. J., 1974. The early diagnosis of Hirschsprung's disease. *Pediatric Radiology*, *2*, 23–28.

Deffrenne, P. D., Daudet, M., and Chappuis, J. P., 1971. Radiological diagnosis of total aganglionosis of the colon. *Annales de Radiologie*, *3–4*, 257–264.

Edelman, S., Strauss, L., Becker, J. M., and Arnheim, E., 1960. Universal aganglionosis of colon. *Surgery*, *47*, 667–677.

Ehrenpreis, T., 1970. *Hirschsprung's Disease* (New Year Book Medical Publishers Inc., Chicago).

Frech, R. S., 1968. Aganglionosis involving the entire colon and a variable length of small bowel. *Radiology*, *90*, 249–257.

Gerald, B., 1965. Aganglionosis of the colon and terminal ileum: Long term survival. *American Journal of Roentgenology*, *95*, 230–234.

Hiatt, R. B., 1951. Pathologic physiology of congenital megacolon. *Annales Surgery*, *133*, 313–320.

Sane, S. M., and Girdany, B. R., 1973. Total aganglionosis coli. Clinical and roentgenographic manifestations. *Radiology*, *107*, 397–404.

Stone, W. D., Hendrix, T. R., and Schuster, M. M., 1965. Aganglionosis of the entire colon in an adolescent. *Gastroenterology*, *48*, 636–641.

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1976, *British Journal of Radiology*, *49*, 34–38

A clinical trial of Amipaque in lumbar myelography

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(*Received May, 1975*)

ABSTRACT

Three hundred lumbar myelographies using a new water-soluble, non-electrolytic contrast medium, Amipaque, were assessed with reference to:

1) the correlation between radiological and operative diagnosis;

(2) the side-effects during and after the myelography.

Myelograms of the same reliability as those obtained with other water-soluble contrast media were obtained. However, arachnoiditis as *sequelae* to previous myelography with oil-soluble and earlier water-soluble contrast media prevented the correct evaluation in some cases.

Spinal anaesthesia was not necessary. There was no case of muscle spasms or other serious complication.

Eight patients who were re-examined with Amipaque more than two months later revealed no evidence of arachnoiditis as *sequelae* to the first Amipaque myelography.

Lumbar myelography with water-soluble contrast media for the demonstration of disc herniation has been used extensively for over 25 years in all Scandinavian and in many Continental countries. The miscibility of the water-soluble contrast media and the cerebrospinal fluid (CSF) results in excellent outlining of the fine structures in the subarachnoid space including the root sleeves, and reliable diagnostic results are obtained. The first contrast medium to be used was Na-monoiodomethane sulphonate (Abrodil, Conturex, Kontrast-U, Methiodal, Skiodan) (Arnell and Lidström, 1931). It was a local irritant and necessitated a spinal anaesthetic.

Iothalamate meglumine (Conray 60 per cent, Conray Meglumine 282, Contrix 28) (Campbell *et al.*, 1964) was considered to be an advance, as spinal anaesthesia was not necessary (Ahlgren, 1969; Præstholm and Lester, 1970, 1972). However, early irritative phenomena in the form of clonic muscle spasms were seen, and a series of reports of complicating fractures of the femur, pelvis and vertebrae, and even death appeared (Irstam *et al.*, 1970; Geller, 1971; Gonsette, 1971; Haase *et al.*, 1973; Christensen, 1974). The dimerization product of iothalamate meglumine, iocarmate meglumine (Dimer-X) seemed to be less convulsive (Gonsette, 1971; Occleshaw and Holyland, 1971; Ahlgren, 1972; Skalpe and Talle, 1973), and at the moment is the water-soluble contrast medium of choice for lumbar myelography in many countries. Recently an increasing number of reports of adhesive arachnoiditis as a late sequel of myelography with water-soluble contrast media have appeared (Autio *et al.*, 1972; Bidstrup, 1972; Halaburt and Lester, 1973; Rådberg and Wennberg, 1973; Ahlgren, 1973/4; Irstam and Rosencrantz, 1973, 1974; Cécile *et al.*, 1974; Irstam, Sundström and Sigsted, 1974; Liliequist and Lundström, 1974). These early and late side-effects have led to the search for better contrast media. The first experimental and clinical reports on the non-dissociable, water-soluble contrast medium metrizamide (Amipaque) have been promising (Skalpe *et al.*, 1973; Grepe, 1974; Hindmarsh, 1974; Klee and Præstholm, 1975) and encouraged us to carry out the clinical trial reported here.

MATERIALS AND METHOD

The material consists of 300 consecutive lumbar myelographies performed on 284 patients in our department during the period November 1973 to November 1974. The sex and age distribution may be seen from Table I.

Premedication consisted of 10 mg of diazapam by mouth the evening before the examination. The lumbar puncture was carried out with the patient seated on the X-ray table using a lumbar-needle with an outer diameter of 1·1 mm. After measurement of the CSF pressure and the removal of 7 ml. CSF for laboratory investigation, the contrast medium was injected. The dose corresponded to 1,360–1,400 mg of iodine. For the first 100 myelographies a solution isotonic with the CSF containing 170 mg of iodine per ml. was used. In the following 200 myelographies, 5 ml. of a solution containing 280 mg of iodine was injected. With this volume we obtained better contrast intensity when the following positioning was used. The films

TABLE I

SEX AND AGE DISTRIBUTION IN 300 AMIPAQUE LUMBAR MYELOGRAPHIES

Age	♂	♀	Total No.	%
≤ 29 years	16	20	36	12
30–44 years	61	48	109	37
45–59 years	63	58	121	40
≥ 60 years	16	18	34	11
Total	156	144	300	100

were taken with the patient lying on the X-ray table, the head-end of which was raised 20 deg. Films were taken in the supine and prone positions, in both oblique positions and in the lateral position with vertical beam. The technique so far was that used in our earlier procedure with Conray myelography as described by Præstholm and Lester, 1970 and Boisen and Lindholmer, 1971.

After the examination the first 200 patients were kept lying in bed with the head-end raised 15 deg. for 24 hours. The following 100 patients had the head end raised 15 deg. for only six hours and afterwards lay flat for a further 18 hours. On the basis of the differences in contrast dose and after-treatment the material can be divided into three groups:

(1) In the first group the dose of Amipaque was 8 ml. (containing 170 mg of iodine per ml.), and the patients were kept with the head-end of the bed raised 15 deg. for 24 hours.

(2) In the second group the dose was 5 ml. (containing 280 mg of iodine per ml.), and the position after the myelography unchanged with the head-end elevated 15 deg. for 24 hours.

(3) In the third group the dose was also 5 ml. (280 mg of iodine per ml.), but the head-end of the bed was raised 15 deg. for only six hours. Afterwards the patients were placed horizontally for 18 hours. These six hours were based on a study of the resorption of Amipaque. On repeated radiographs the contrast had disappeared or could just be identified in the base of the sacral sac after six hours.

A questionnaire was filled in for each patient. The first part of this concerned the doctor's report of the examination procedure including the patient's complaints during the injection of the contrast medium. The second part consisted of a doctor's interview of the patient more than 24 hours after the myelography. The duration of any complaints was registered.

All myelograms have been evaluated without knowledge of either clinical or operative findings.

The following criteria for diagnosis were used: Disc herniation (prolapse) was diagnosed when a root pocket was shorter than the contralateral root pocket, most often accompanied by a local antero-lateral indentation in the contrast column and dislocation of a filum radiculare (Hirsch, Rosencrantz and Wickbom, 1969).

A marked rounded defect behind a disc in the ventral contour of the contrast column without shortening of root pockets was called a disc protrusion.

Post-operative scar tissue was characterized by a local, serrated defect in a root pocket or in the contrast column.

In adhesive arachnoiditis there was concentric narrowing of the sacral sac and obliteration of lumbar and/or sacral root pockets. Often the longitudinal striation of the contrast column due to the fila radicularia had disappeared.

TABLE II

RADIOLOGICAL DIAGNOSES AND OPERATIVE FINDINGS

Radiology			Operation							
Diagnosis	No.	No operation	Normal	Prolapse	Protrusion	Spondylolisthesis	Scar tissue	Adhesive arachnoiditis	Other findings	No.
Normal	70	59	8	3						11
Prolapse	165	11	2	143	2		3	1	3	154
Protrusion	32	22		4	6					10
Spondylolisthesis	3	0				3				3
Scar tissue	11	5		2			4			6
Adhesive arachnoiditis	17	8		4				5		9
Unsuccessful	2	2								0
Total	300	107								193

RESULTS OF MYELOGRAPHY

In 70 patients the myelogram was evaluated as normal (Table II). Eleven of these patients were operated upon on clinical indications. In eight patients the operative findings were normal. In three patients a prolapse was found: one paramedian from the third lumbar disc, and two anterolateral prolapses from the fifth lumbar disc, one of which was dislocated 3 cm away from its disc down into the sacral canal.

In 228 patients a positive radiological diagnosis was made. Operation was performed on 182 of these patients. In 161 patients the radiological diagnosis was confirmed at operation. In further 13 patients there was good agreement between the radiological picture and the operative findings, but there were difficulties in diagnosing the actual lesion: in ten patients it was not possible to differentiate between a prolapse and scar tissue or adhesive arachnoiditis as *sequelae* of earlier operations and myelographies, and in three patients lesions other than a prolapse were found to obliterate the root pocket, *viz.*, a swollen nerve root in one patient found to have a radiculitis, granulation tissue from a discitis, and extradural varices. In eight patients there was disagreement between the positive radiological diagnosis and the operative findings: four suspected prolapses were not found at operation (two discs were normal and two only protruding). Four protrusions were found to be prolapses; two of these were paramedian.

SIDE EFFECTS DURING AND AFTER MYELOGRAPHY

Four patients complained of pain in one leg during the lumbar injection of Amipaque. Otherwise there were no immediate reactions to the injection, in particular there was no evidence of fall in blood pressure.

TABLE III

COMPLAINTS AFTER LUMBAR MYELOGRAPHY WITH AMIPAQUE (300 CASES)

	No. of patients	%
Headache	128	43
Nausea	30	10
Vomiting	9	3
Dizziness	22	7
Tinnitus	4	
Diplopia	2	
Lumbar pain	12	4
Pain or paraesthesia in the legs	14	5
Jerks in the legs	1	
Retention of urine	14	5

After myelography 161 of 300 patients had one or more complaints. The most common of these was headache, which occurred in 128 patients (Table III). Every patient was examined for nuchal rigidity, which was never found. In 29 per cent of these cases the headache began within six hours of the examination, in 37 per cent between 6 and 24 hours, and in 34 per cent later than 24 hours. In 48 per cent a relationship between the upright position and the headache was mentioned. The headache often began when the patient was allowed to get out of bed 24 hours after myelography. The duration of the headache is shown in Table IV. As there was no direct relationship between the duration and the severity of the headache, we have graduated the headache according to the patient's activity in the post-myelographic period. In 52 per cent of 62 patients with headache it was slight and did not interfere with the patient's normal activity in the ward or at home at the weekend. In a further 10 per cent a mild analgesic provided sufficient relief. In 38 per cent the headache was severe and kept the patient in bed. One-half of these patients were free of headache when lying flat, whilst in the other half there was amelioration.

Thirty patients had nausea for a short period, nine vomited.

Twenty-two patients complained of dizziness. For this reason the blood pressure was measured before and repeatedly for four hours after the myelography in 25 patients; no fall in blood pressure was observed.

One patient, who clinically had a right peroneal paresis and radiologically a normal myelogram, complained of lumbar pain and jerks in his right leg on the day after myelography. The jerks were not observed by us or by the staff on the ward. No patient had muscle spasms of the type observed after Conray and Dimer-X myelography.

TABLE IV

DURATION OF HEADACHE IN 128 PATIENTS AFTER AMIPAQUE LUMBAR MYELOGRAPHY

	No.	%
<6 hours	30	23
6–24 hours	22	17
24–72 hours	24	19
>72 hours	47	37
unknown	5	4
Total	128	100

Eight patients were re-examined with Amipaque after 2–11 months. There were no signs of complicating adhesive arachnoiditis.

DISCUSSION

The diagnostic reliability of lumbar Conray myelography was demonstrated by, among others, Ahlgren, 1969, and Præstholm and Lester, 1970. They found good correlation between the myelographic and operative findings in 96 and 97 per cent of 99 and 78 cases, respectively. In the present material of 193 operated patients there was agreement between myelogram and operation in 94 per cent. In three of the 11 cases with disagreement a paramedian prolapse was found. In a further 6 per cent of cases it was difficult to differentiate between post-myelographic or post-operative changes and a prolapse. These changes were seen after Pantopaque myelography and high-dose Conray myelography, and after Abrodil and Conray myelography followed by operation. The clinical importance of these alterations is still questionable, but their disturbance of the myelogram is evident. These difficulties have already been described by Fahrenkrug, Gottschalck and Højgaard in 1963. However, they described the changes as being solely post-operative.

No serious complications were seen in connection with Amipaque myelography. In particular there was no case of spasms in the lower extremities or convulsions, such as those seen after Conray and Dimer-X myelography. A high incidence of headache was rather troublesome. The time of occurrence, sex and age distribution with dominance of younger females, and the nature of this headache had the characteristics of the post-lumbar-puncture headache, but the incidence was somewhat higher than usually described (Tourtelotte *et al.*, 1964). On the assumption that a relationship existed between the post-myelographic positioning with the head-end raised and the high incidence of headache because of an increased leakage of CSF from the puncture hole in the meninges, we cut down the time with the head-end raised from 24 to 6 hours in the last 100 patients. In comparable groups consisting of the male patients we found an increase in the number of patients with headache from 18 out of 54 patients positioned with elevated head-end for 24 hours to 18 out of 36 patients with elevated head-end for only six hours. This unexpected increase in the frequency of headache indicates that conditions other than the leakage of CSF are involved in the occurrence of headache. There may well be a direct contrast-medium action on the central nervous tissue depending on concentration and exposure time.

CONCLUSION

This investigation shows that Amipaque is a contrast medium which fulfils many of the demands made of the ideal contrast medium for myelography (Di Chiro and Fisher, 1964). Like Conray and Dimer-X it can be used without spinal anaesthesia, and the resorption time makes supplementary films possible. Good visualization of the fila radicularia and root pockets is obtained, and ensures reliable diagnostic results. In contrast to Conray and Dimer-X no serious immediate side-effects and as yet no late *sequelae* have been seen.

We therefore recommend the substitution of Amipaque for the contrast media hitherto employed for lumbar myelography in lumbago-sciatica.

REFERENCES

Ahlgren, P., 1969. Lumbale Myelographie mit Conray Meglumin 282. *Fortschritte auf dem Gebiete der Röntgenstrahlen, 111*, 270–276.

1972. Dimer-X. A new contrast medium for lumbar myelography without spinal anaesthesia. *Acta radiologica, 13*, 753–761.

1973/4. Long term side effects after myelography with watersoluble contrast media: Conturex, Conray Meglumin 282 and Dimer-X. *Neuroradiology, 6*, 206–211.

Arnell, S., and Lidström, F., 1931. Myelography with Skiodan (Abrodil). *Acta radiologica, 12*, 287–288.

Autio, E., Suolanen, J., Norrbäck, S., and Slätis, P., 1972. Adhesive arachnoiditis after lumbar myelography with meglumine iothalamate (Conray). *Acta radiologica, 12*, 17–24.

Bidstrup, P., 1972. A case of chronic adhesive arachnoiditis after lumbar myelography with methiodal-sodium. *Neuroradiology, 3*, 157–159.

Boisen, E., and Lindholmer, E., 1971. Serious complications of myelography with meglumine iothalamate [in Danish]. *Nordisk medicin, 85*, 520–524.

Bull, J., 1971. Myelography. *Neuroradiology, 2*, 1–2.

Campbell, R. L., Campbell, J. A., Heimburger, R. F., Kalsbeck, J. E., and Mealey, J., 1964. Ventriculography and myelography with absorbable radiopaque medium *Radiology, 82*, 286–289.

Cécile, J. P., Regnier, G., Guaquière, A., Doffiny, L., and Cuvelier, A., 1974. Postural protection against complications in radiculography with Dimer-X. *Neuroradiology, 7*, 167–172.

Christensen, A. B., 1974. Fracture of the neck of the femur as a complication of Conray myelography [in Danish]. *Ugeskrift for læger, 136*, 1579–1580.

Di Chiro, G., and Fisher, R. L., 1964. Contrast radiography of the spinal cord. *Archives of Neurology, 11*, 125–143.

Fahrenkrug, A., Gottschalck, B., and Højgaard, K., 1964. Myelography with water-soluble media in lumbago-sciatica after operation for herniated lumbar disk. *Acta radiologica, 2*, 138–144.

Geller, G., 1971. Komplikationen bei der lumbale Myelographie mit Conray 282 (Contrix 28). *Fortschritte auf dem Gebiete der Röntgenstrahlen, 114*, 568–569.

Gonsette, R., 1971. An experimental and clinical assessment of water-soluble contrast medium in neuroradiology. A new medium—Dimer-X. *Clinical Radiology, 22*, 44–56.

Grepe, A., 1974. Examination of intracranial basal cisterns with water-soluble contrast medium. (Thesis, Stockholm).

Haase, J., Jepsen, B. V., Bech, H., and Langebæk, E., 1973. Spinal fracture following radiculography using meglumine iothalamate (Conray). *Neuroradiology, 6*, 65–70.

Halaburt, H., and Lester, J., 1973. Leptomeningeal changes following lumbar myelography with water-soluble contrast media (meglumine iothalamate and methiodal sodium). *Neuroradiology, 5,* 70–76.

Hindmarsh, T., 1974. Myelography with a non-ionic water-soluble contrast medium (Metrizamide). (Thesis, Stockholm).

Hirsch, C., Rosencrantz, M., and Wickbom, I., 1969. Lumbar myelography with water-soluble contrast media with special reference to the appearances of root pockets. *Acta Radiologica, 8,* 54–64.

Irstam, L., Lönnerholm, T., Sundström, M., and Zsigmond, M., 1970. Lumbar myelography with Conray Meglumin 282. [in Swedish]. *Läkartidningen, 67,* 3185–3190.

Irstam, L., and Rosencrantz, M., 1973. Water-soluble contrast media and adhesive arachnoiditis. I. Reinvestigation of nonoperated cases. *Acta Radiologica, 14,* 497–506.

1974. Water-soluble contrast media and adhesive arachnoiditis. II. Reinvestigation of operated cases. *Acta Radiologica, 15,* 1–15.

Irstam, L., Sundström, R., and Sigstedt, B., 1974. Lumbar myelography and adhesive arachnoiditis. *Acta Radiologica, 15,* 356–368.

Klee, J. G., and Præstholm, J., 1975. Comparison of iothalamate meglumine, metrizamide and iodophendylate in cerebral ventriculography. *Investigative Radiology, 10,* 244–250.

Liliequist, B., and Lundström, B., 1974. Lumbar myelography and arachnoiditis. *Neuroradiology, 7,* 91–94.

Occleshaw, J. V., and Holyland, J. N., 1971. Comparative study of the effects of Conray 280 and Dimer X in lumbar radiculography. *British Journal of Radiology, 44,* 946–948.

Præstholm, J., and Lester, J., 1970. Water-soluble contrast lumbar myelography with meglumine iothalamate (Conray). *British Journal of Radiology, 43,* 303–308.

1972. Complications of myelography with Conray Meglumin. *Acta Radiologica, 13,* 860–864.

Rådberg, C., and Wennberg, E., 1973. Late sequelæ following lumbar myelography with water-soluble contrast media. *Acta Radiologica, 14,* 507–512.

Skalpe, I. O., and Talle, K., 1973. Lumbar radiculography with meglumine iocarmate (Dimer-X). *Journal of the Oslo City Hospitals, 23,* 121–127.

Skalpe, I. O., Torbergsen, T., Amundsen, P., and Presthus, J., 1973. Lumbar myelography with metrizamide. *Acta Radiologica, Supplementum 335,* 367–379.

Tourtelotte, W. W., Haerer, A. F., Heller, G. L., and Somers, J. E., 1964. *Post-lumbar puncture headaches* (Charles C. Thomas, Springfield, Illinois).

Book review

Laboratory facilities and working procedures for the hospital preparation of radiopharmaceuticals, edited by D. M. Taylor, P. H. S. Smith and N. G. Trott, pp. v + 58. 1975.
(Royal Marsden Hospital and Institute of Cancer Research) Sutton. Price £1·00.

This pamphlet reports the proceedings of a one-day forum arranged by the Departments of Radiopharmacology and Physics of the Royal Marsden Hospital to discuss the problems arising from the preparation of radiopharmaceuticals in hospitals and to exchange views and information. It was attended by 23 physicists, 18 pharmacists, 7 nuclear medicine consultants, 4 technicians and 3 chemists. Apparently there were no hospital microbiologists present, with the result that the main discussion was on sterility and related problems and the radiation physics and protection aspects received relatively cursory attention.

This document must be regarded as required reading for anyone who is involved in any way in the administration of radioactive materials to hospital patients. Starting from a review by Dr. D. H. Keeling on adverse reactions to radiopharmaceuticals, it focuses attention on the main current problems. There follow several prepared papers on laboratory facilities and working procedures, but the greater part of the report covers the free-for-all discussion. This makes stimulating reading, but is lacking in objective and clear cut conclusions, since it appears that only the clinicians present were able to take an overall view of the problem in its wider context. However, as a result of this meeting, a working party has been set up to produce guidelines on radiopharmaceutical preparation, and its report will be available in due course. Meanwhile, the present document is best regarded as useful background material.

In the period around 1950 many hospitals obtained irradiation units from Harwell, and sterile materials, including labelled cells and proteins as well as short-lived isotopes, were prepared and used as a matter of course. One went to one's colleagues in the bacteriology department to learn the simple techniques which have been developed since the days of Pasteur for dealing safely with virulent pathogens. During the subsequent halcyon period, when everything could be bought off the shelf, a new generation has grown up and the old skills seem to have been lost. Unfortunately, it seems from the discussion at this meeting that there is a widespread impression that grandiose accommodation, facilities and titles, backed by duly appointed inspectors, can replace sound basic training of the operator, some native skill and elementary intelligence plus meticulous care. If this view prevails it augers ill for the patient, not to mention the taxpayer.

N. Veall

1976, *British Journal of Radiology*, *49*, 39–42

The "central lucency" sign of lobar dysmorphism (pseudotumour of the kidney)

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(Received April, 1975 and in revised form June, 1975)

ABSTRACT

A proved case of pseudotumour of the kidney due to lobar dysmorphism showed a "central lucency" sign, differentiating this developmental variant from an enlarged column of Bertin. This sign is described in a further case.

King, Friedenberg and Tena (1968) described a developmental pseudotumour of the kidney due to an excessive infolding of cortical tissue. This presents as a localized mass, usually situated between the infundibula of the upper and middle calyceal groups, and has been variously called "prominent or enlarged column of Bertin" (Azimi and Bryan, 1974; Felson and Moskowitz, 1969; Green *et al.*, 1972; Hartman and Hodson, 1969; King *et al.*, 1968; Lopez, 1970; Meaney, 1969), "prominent renal column" (Braunstein *et al.*, 1972), "benign cortical rest" (Flynn and Gittes, 1972), "focal cortical hyperplasia" (Popky *et al.*, 1969) and "renal pseudotumour" (Gooding, 1971; Simon, 1970). Charghi and his colleagues (1971) described a similar congenital anomaly which they called malposition of a renal lobe or lobar dysmorphism, in which not only cortex but also medulla were found deep within the kidney. Both these developmental variants are thought to be due to an abortive attempt at duplication of the renal parenchyma (Azimi and Bryan, 1974; Charghi *et al.*, 1971; Green *et al.*, 1972; Hartman and Hodson, 1969; King *et al.*, 1968; Lopez, 1970).

A further proved case of pseudotumour of the kidney due to lobar dysmorphism is presented, together with a second case. A radiological sign which differentiates this condition from an enlarged column of Bertin is described and correlated with the histological appearances.

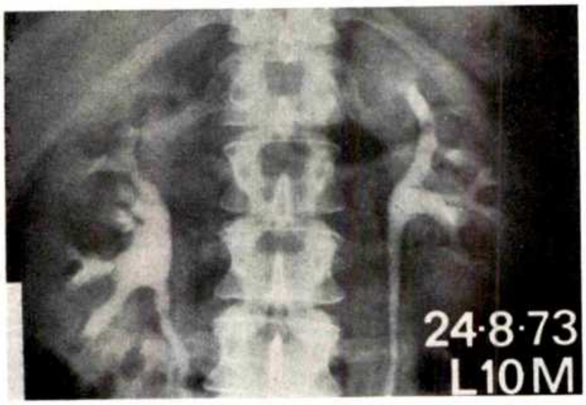

FIG. 1. *Case 1.*

Ten-minute IVU film showing a mass in the centre of the right kidney with splaying of the adjacent infundibula.

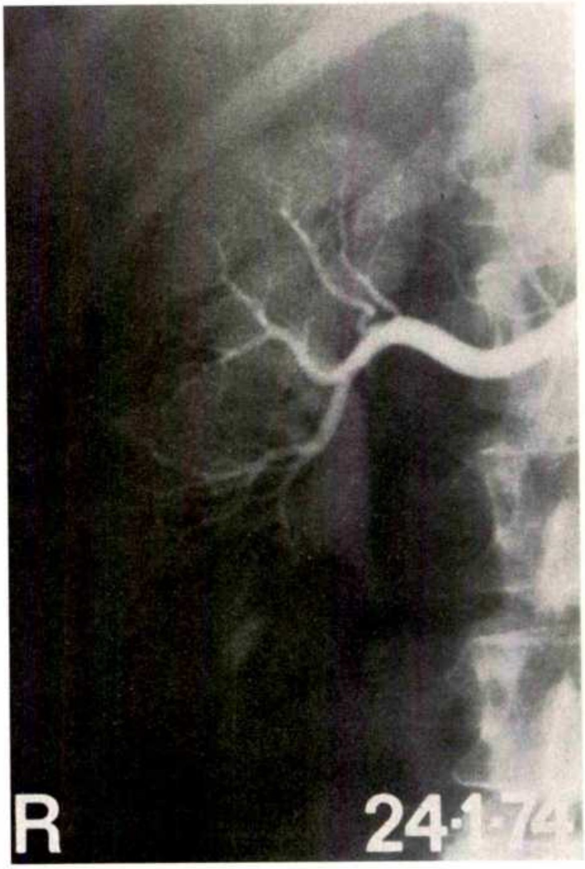

FIG. 2. *Case 1.*

Right selective renal arteriogram: arterial phase: antero-posterior. Showing slight displacement of the interlobar arteries by the central mass. (The lower pole was supplied by an accessory vessel arising from the aorta just proximal to the bifurcation.)

CASE REPORTS

Case 1

A 52-year-old woman presented in August 1973 with a four-month history of intermittent painless haematuria. Urography (Fig. 1) demonstrated slight splaying of the infundibula of the upper and middle calyces of the right kidney by an apparent central mass, associated with a short middle calyx. The appearances were thought to be due to a pseudotumour. Urine cytology and cystoscopy were normal. Urine culture showed a significant growth of coliform bacilli. Following a course of Co-trimoxazole her urine became sterile.

In January 1974 angiography was performed because of persistent haematuria. The arterial phase (Fig. 2) demonstrated slight displacement of the interlobar vessels by the central mass, which, in the nephrogram phase, showed a dense blush surrounding a clearly defined central lucency (Fig. 3). No pathological vessels were seen, even after noradrenalin. The angiographic appearances were those of a pseudotumour. It was postulated that the radiolucency represented centrally placed medulla within the malpositioned cortex.

Malignant cells were found in the urine for the first time in September 1974. Repeat urography demonstrated cut-off of the infundibulum of the right upper calyceal group. A diagnosis of transitional cell carcinoma was made and a right nephroureterectomy was performed. Pathological examination confirmed the presence of a transitional cell carcinoma involving the upper calyces. The mass in the centre of the kidney was a pseudotumour due to lobar dysmorphism, composed of normal renal cortical tissue surrounding a central core of medulla (Fig. 4). There was an associated small draining calyx.

Case 2

A 37-year-old man was found in July 1974 to be hypertensive with left ventricular hypertrophy and retinopathy. Urinalysis was normal. Urography (Fig. 5) suggested the presence of a mass in the centre of the right kidney. Angiography demonstrated slight stretching of the interlobar arteries around the mass, which showed a dense blush containing a central lucency in the nephrogram phase (Fig. 6). The left kidney was normal and no renal cause for the hypertension was found. The right kidney was not explored as the appearances were thought to be those of lobar dysmorphism. He responded to hypotensive drugs and has remained well.

DISCUSSION

Both patients show the well-documented urographic and angiographic features of developmental pseudotumour of the kidney: an apparent mass causing slight splaying of the infundibula of the upper and middle calyces, some form of duplication of the collecting system, a small draining calyx, splaying of the interlobar arteries around the mass, and a

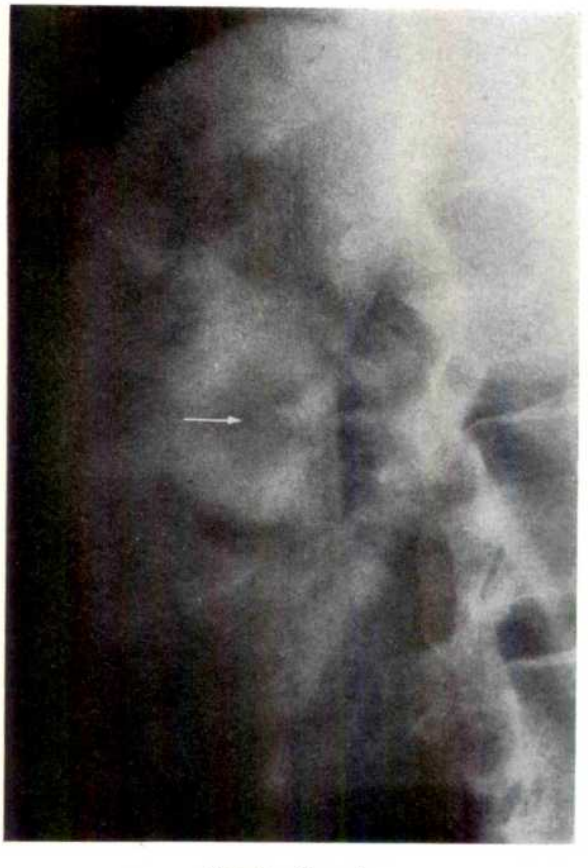

FIG. 3. *Case 1.*

Right selective renal arteriogram: nephrogram phase: LPO. Showing a dense blush surrounding a central lucency, the "central lucency" sign (arrow).

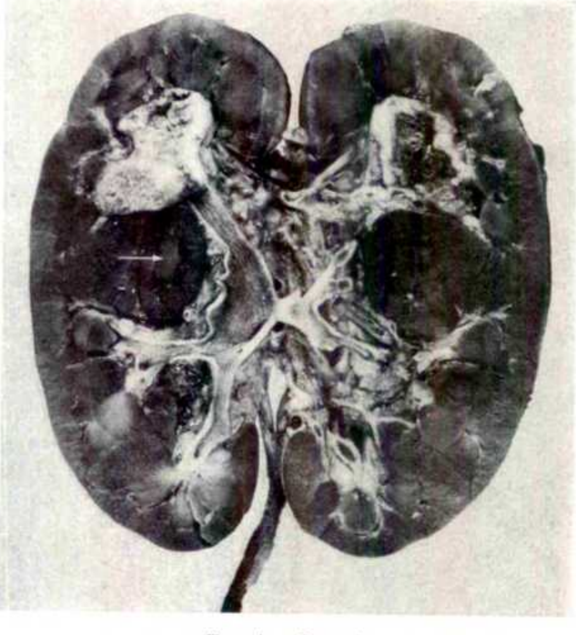

FIG. 4. *Case 1.*

Longitudinal section through the right kidney showing a transitional cell carcinoma involving the upper calyces and a pseudotumour due to lobar dysmorphism in the centre of the kidney, darker cortex surrounding the paler medulla (arrow).

dense blush in the nephrographic phase of the arteriogram. However, in addition, both cases showed a clearly-defined radiolucent area within the dense blush, the "central lucency" sign, which in one patient (Case 1) proved to be due to centrally placed medulla within the malpositioned cortex. The "central lucency" sign thus indicated lobar dysmorphism.

There is one previous report describing a central lucency in an unproven case of lobar dysmorphism (Charghi *et al.*, 1971). However, the appearance is probably not uncommon, for review of the literature has revealed several cases of pseudotumour of the kidney in which the "central lucency" sign is illustrated, although not described (Popky *et al.*, 1969; Simon, 1970). The same appearance, described by Flynn and Gittes (1972), proved to be due to a benign cyst within a large cortical rest.

It is essential to recognize pseudotumours due to normal renal tissue in order to avoid unnecessary surgery. There has been recent emphasis on techniques such as nephrotomography (Azimi and Bryan, 1974; Green *et al.*, 1972) and scintigraphy (Braunstein *et al.*, 1972) to make the diagnosis. On nephrotomography a pseudotumour due to an enlarged column of Bertin is of homogeneous density equal to or greater than that of the surrounding parenchyma. Nephrotomography was not carried out in either of our cases but it is not unreasonable to assume that the presence of centrally-placed medulla within the malpositioned cortex might affect the uniform density of the mass.

Although the "central lucency" sign may be due to a cyst within a cortical rest (Flynn and Gittes, 1972), the present evidence suggests that it is more likely to indicate a pseudotumour due to lobar dysmorphism. In cases where there is doubt as to the nature of a central mass this sign provides useful confirmatory evidence of pseudotumour of the kidney.

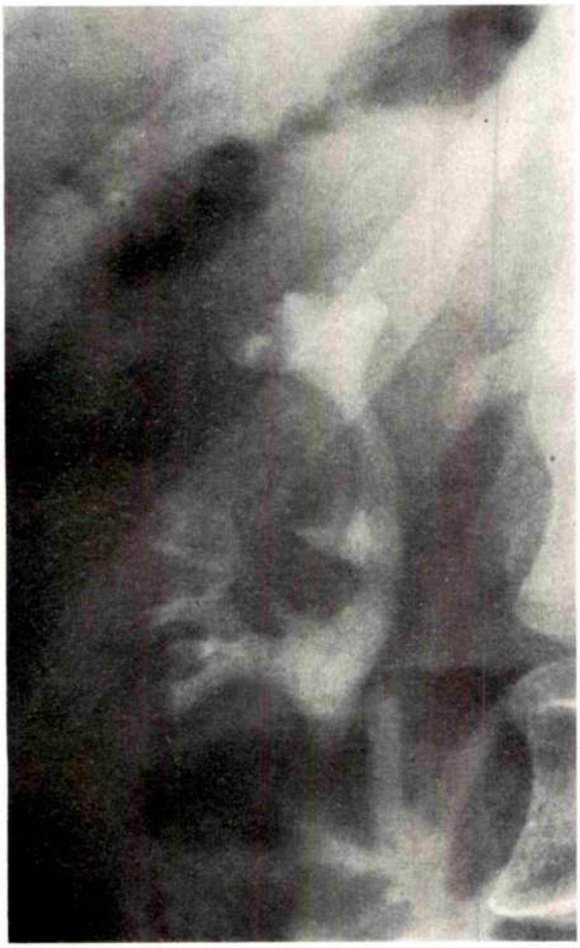

FIG. 5. *Case. 2.*

IVU film: RPO. Showing an apparent mass in the centre of the right kidney.

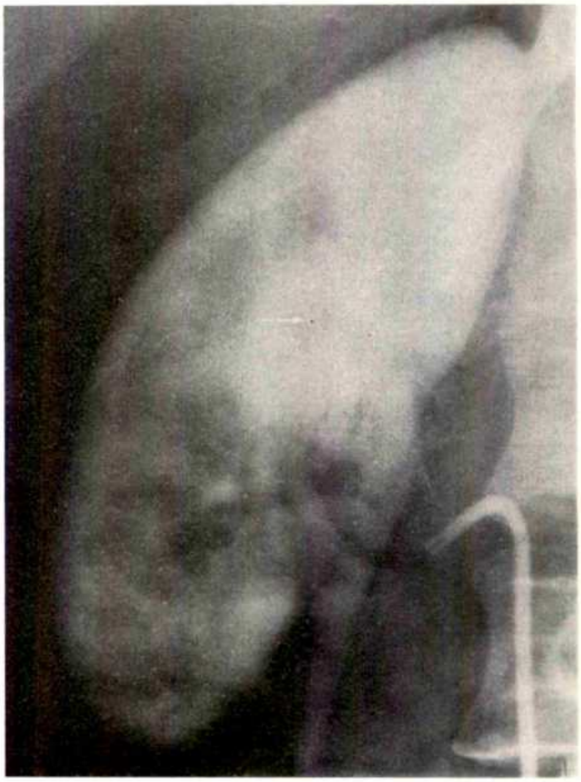

FIG. 6. *Case 2.*

Right selective renal arteriogram: nephrogram phase: RPO Showing the "central lucency" sign (arrow).

ACKNOWLEDGMENTS

I would like to thank Mr. W. F. Hendry for permission to publish details of the patient (Case 1) under his care. I am grateful to Dr. I. Kelsey Fry for his help and advice in the preparation of the text. The photographs were kindly provided by the Department of Medical Illustration, St. Bartholomew's Hospital.

REFERENCES

AZIMI, F., and BRYAN, P. J., 1974. Familial occurrence of renal pseudotumour due to enlarged column of Bertin in two brothers and their first cousin. *Clinical Radiology*, *25*, 467–474.

BRAUNSTEIN, P., HERNBERG, J. G., BOSNIAK, M. A. and BARASCH, E., 1972. Scintiscan evaluation of prominent renal columns. *Radiology*, *104*, 103–106.

CHARGHI, A., DESSUREAULT, P., DROUIN, G., GAUTHIER, G. E., PERRAS, P., ROY, P., and CHARBONNEAU, J., 1971. Malposition of a renal lobe (lobar dysmorphism): a condition simulating renal tumor. *Journal of Urology*, *105*, 326–329.

FELSON, B., and MOSKOWITZ, M., 1969. Renal pseudotumors: the regenerated nodule and other lumps, bumps and dromedary humps. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*,, *107*, 720–729.

FLYNN, V. J., and GITTES, R. F., 1972. Benign cortical rest: a "pseudotumor" of the kidney. *Journal of Urology*, *108*, 54–57.

GOODING, C. A., 1971. Childhood renal pseudotumor. *Radiology*, *98*, 79–80.

GREEN, W. M., PRESSMAN, B. D., MCCLENNAN, B. L., and CASARELLA, W. J., 1972. "Column of Bertin": diagnosis by nephrotomography. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *116*, 714–723.

HARTMAN, G. W., and HODSON, C. J., 1969. The duplex kidney and related abnormalities. *Clinical Radiology*, *20*, 387–400.

KING, M. C., FRIEDENBERG, R. M., and TENA, L. B., 1968. Normal renal parenchyma simulating tumor. *Radiology*, *91*, 217–222.

LOPEZ, F. A., 1970. Renal pseudotumors. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *109*, 172–184.

MEANEY, T. F., 1969. Errors in angiographic diagnosis of renal masses. *Radiology*, *93*, 361–366.

POPKY, G. L., BOGASH, M., POLLACK, H., and LONGACRE, A. M., 1969. Focal cortical hyperplasia. *Journal of Urology*, *102*, 657–660.

SIMON, H., 1970. Renal pseudotumor: a case report. *Journal of Urology*, *104*, 45–46.

Book review

N.C.R.P. REPORT, No. 43, 1975. Review of the Current State of Radiation Protection Philosophy. (Recommendations of the National Council on Radiation Protection and Measurement), pp. v + 50.

This report is a position statement by the NCRP following the publication of two reports, one by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1972) and the other by the National Academy of Sciences Advisory Committee on the Biological Effects of Ionising Radiations (NAS-BEIR, 1972). While the two 1972 reports are based on the same data, they often draw different conclusions and make different assessments of the biological effects of radiation. The NCRP therefore decided to review these reports "for the purpose of identifying differences, their significance, and especially how they relate to the NCRP's recommendations relative to permissible exposures or dose limits for the public". One of the major issues is the formulation of risk estimates at low doses and low dose-rate by extrapolation from dose-incidence curves at high dose and high dose rates.

In Chapter 2, which deals with the current position of the NCRP, it is made clear that they continue to hold the view that risk estimates made in this way cannot be expected to provide realistic estimates of actual risks at low levels and that resulting estimations could, therefore, be of only marginal value. The remainder of this chapter discusses the relationship of risk estimates in relation to the benefits to society and concludes that before considering further restriction of radiation protection standards it is important to attain realistic values for risk.

The similarities and differences between the two 1972 reports are analysed in Chapter 3. Many similarities exist as, for example, that risk estimates per unit dose in the range of observed data are derived from a linear hypothesis and the likelihood of no absolute dose threshold for carcinogenic and genetic effects. The NAS-BEIR report differs in that it presents numerical estimates of risk at levels well below the observed data levels extrapolating by factors of 10^3 in dose and 10^9 in dose-rate. Differences in the utilization of data regarding the variation of neutron RBE with dose are also discussed.

The final chapter is an historical review of the subject of the report and its relationship to dose limits to the population.

Although some of the discussions in this report tend to be rather repetitive, it attempts and succeeds in its attempt to outline current policy and the dangers of using present data in making risk-benefit evaluations.

T. BRYANT.

1976, *British Journal of Radiology*, *49*, 43–49

Factors involved in the detection of pulmonary emboli by labelling techniques

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(*Received September, 1974 and in revised form January, 1975*)

ABSTRACT

Experiments were set up to assess quantitatively the problem of detecting, by scanning and gamma-camera, labelled pulmonary emboli in the presence of background radioactivity. *In vitro*, a relative concentration of radioactivity of 2:1 was required to detect a 1·1 cm diameter "hot spot".

The results *in vivo* suggest that the level of radioactivity of a pulmonary embolus situated in the centre of the lung field should be at least six times that of the circulating blood.

Although lung scanning with ^{99}Tc^{m}-MAA has become an established procedure for the detection of pulmonary emboli, it has been shown that other disease processes can produce similar scan abnormalities (Linton *et al.*, 1971). In order to improve the accuracy of diagnosis of pulmonary embolism, many attempts have been made to visualize an embolus as a "hot spot" using a specific radiochemical label. A variety of radiopharmaceuticals have been tested in experimental thrombo-embolic situations; these include ^{131}I or ^{99}Tc^{m}-labelled plasminogen (Gomez *et al.*, 1963); plasmin (Ouchi and Warren, 1962); fibrinogen/fibrin antibody (Spar *et al.*, 1969); streptokinase(Dugan *et al.*, 1973), urokinase (Rhodes; *et al.*, 1972); and leucocytes (Kwaan and Grumet, 1972). Many of these compounds have been effective for embolus detection at the experimental stage, but clinical application to pulmonary embolus diagnosis has not been convincing.

Recent studies *in vitro* and *in vivo* (Scully, Strachan and Kakkar, 1973; Strachan, Scully and Kakkar, 1974) have shown ^{131}I-plasminogen to possess a significant affinity for formed emboli and thrombi. However, the concentration of ^{131}I-plasminogen into emboli to a level of four times blood background was insufficient for the detection of embolus using a gamma-camera. This failure was probably due to the difficulty of detecting the labelled emboli against the circulating background radioactivity. A series of experiments was carried out in dogs to determine some of the factors involved in "hot-spot" visualization. In these experiments, artificial pulmonary emboli were detected in situations where the quantitative relationship between the total radioactivity in the embolus and that of the circulating blood was known.

METHODS AND MATERIALS

"*In vitro*" studies

A standard Williams phantom was used with wells of 0·6, 1·1, 1·9 and 3·8 cm diameter and 1·8 cm depth. These "hot spots" were surrounded by a background radiation with the same concentration of radioactivity, but 0·9 cm in depth. The phantom was filled with a solution of ^{99}Tc^{m} (pertechnate, 4 μCi.ml^{-1}) and scanned with a Picker Magnascanner V fitted with a coarse focus collimator, Type No. 2111. The control plane of the phantom was set at the focus of the collimator (5 in. in air). Photographs of the phantom were also made using a gamma-camera (Phogamma, Nuclear Chicago) fitted with a 140 keV high resolution collimator.

"*In vivo*" studies

Two sets of experiments were performed: artificial emboli were prepared containing a known total amount of radioactivity. These were introduced into the dogs and the quantitative relationship between the embolus radioactivity and the radioactivity of the blood was followed continuously. The relationship was expressed as an embolus activity volume equivalent (EAVE), namely that volume (ml.) of blood with an activity equal to that of the embolus.

Method A. Two greyhound dogs were anaesthetized with sodium phenobarbitone and 200 μCi ^{131}I-human serum albumin (Radiochemical Centre, Amersham, U.K.) were injected intravenously. After equilibration the labelled albumin provided a fairly constant blood background throughout the four-hour course of the experiment. A known volume of blood was taken and counted in a scintillation counter (NaI well). Artificial emboli were prepared from 1·5 to 2·0 cm lengths of 20 G bore tubing from an infant scalp vein set (Abbott, U.S.A.).

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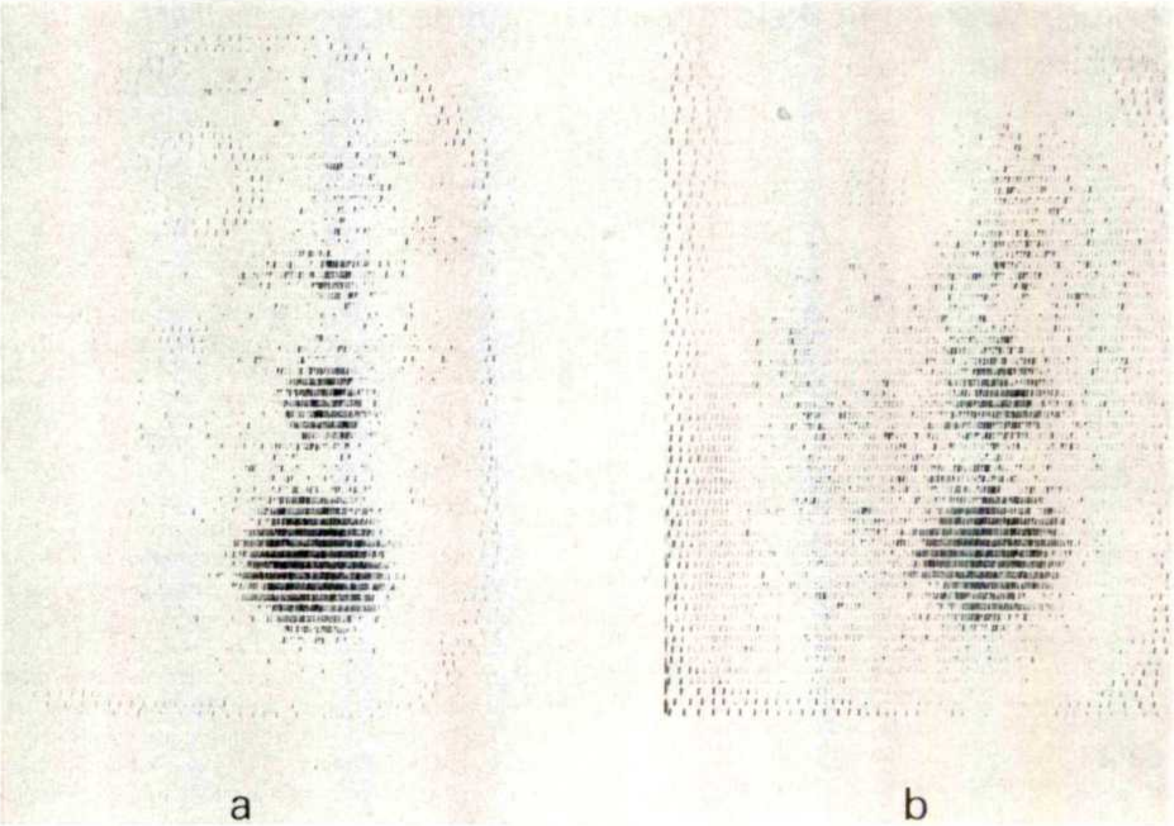

FIG. 1.
Picker scan of a Williams phantom alone (a) and overlaid with a uniform phantom (b).

These were heat sealed at one end and the required quantity of ^{131}I solution instilled, followed by a similar volume of a radio-opaque solution (Hypaque). The other end of the tube was sealed and the tube embolised via the femoral vein. The positioning of the embolus in the pulmonary arterial tree was determined by radiography (Fig. 2a). The thorax was scanned with a Picker Magnascanner at a speed of 70 cm/min^{-1} and the scans visually assessed for the presence of "hot spots". The data was concurrently recorded for storage and analysis off-line by an ICL-1905E computer.

Method B. Two greyhound dogs were used after preliminary determination of their blood volume using the ^{113}In^{m} transferrin technique. Emboli were prepared as described above, but containing ^{99}Tc^{m}. After embolization, Polaroid prints were made of the embolus using a Phogamma gamma-camera. ^{99}Tc^{m} was injected intravenously in sufficient dosage to make the embolus invisible against the lung background (Fig. 3a). Serial prints were made at 30-minute intervals for six hours, and as the blood background fell, the time at which the "hot spot" reappeared was noted (Fig. 3b). Blood samples were taken continuously to determine the embolus activity volume equivalent (Fig. 4).

Scan and print analysis. Scans and prints were also examined to determine the recorded count-rates associated with the embolus and an equal area of background. The ratio/embolus count-rate: background count-rate was correlated with changes in EAVE.

(1) Scans: Similar areas of heart, lung and embolus radioactivity were marked out on the computer print-out of each scan (2c, 2f). The total count associated with each area was then computed.

(2) Phogamma pictures: Negatives of the Polaroid prints were prepared and estimates of the maximum

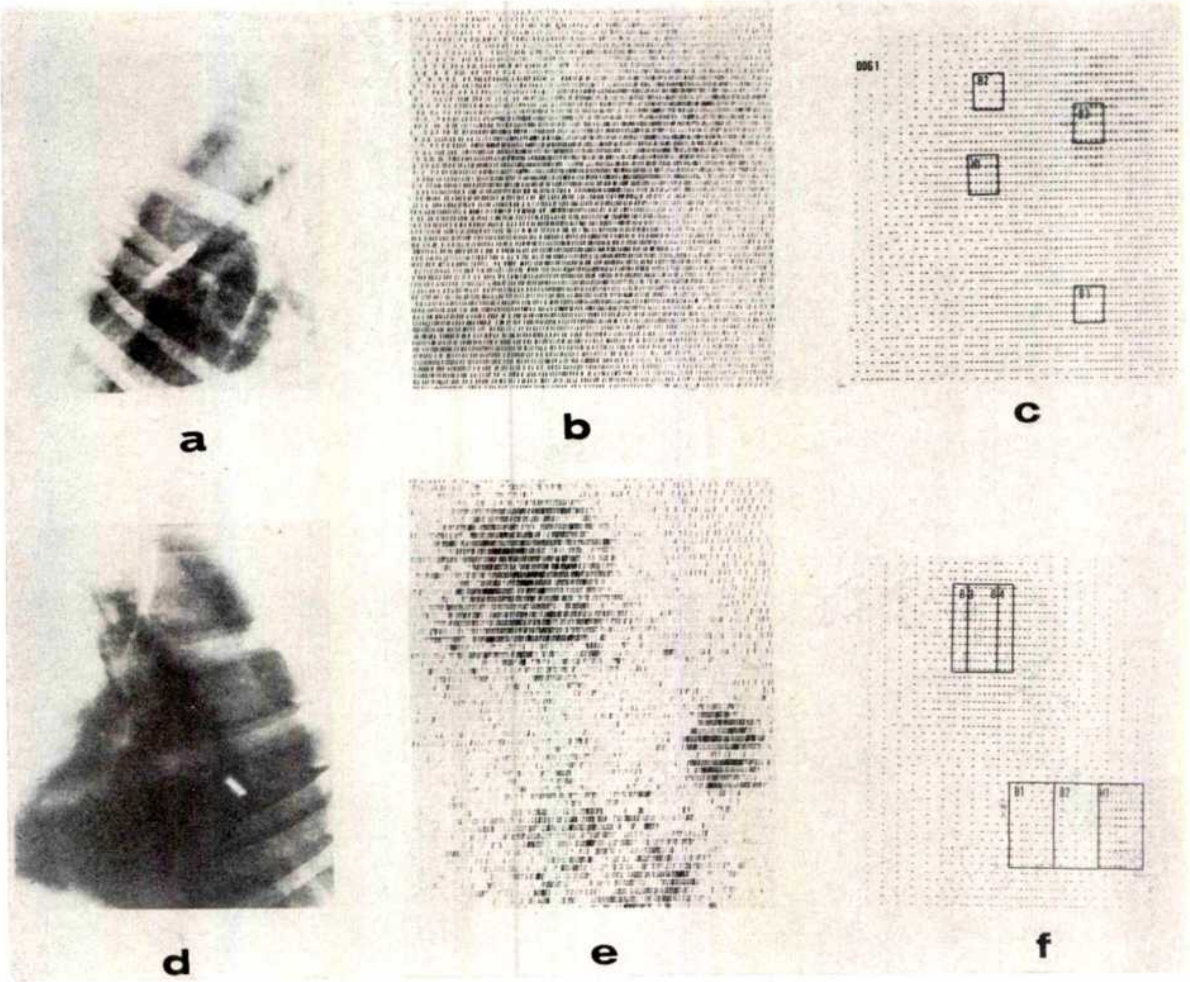

FIG. 2.

Radiograms (a, d), Picker scans (b, e), and computer print-out of the scans (c, f) of the heart, lung region of Dogs 1 and 2 respectively.

film density associated with areas of the heart, lung, liver and embolus were made with a densitometer (Baldwin Instruments, Kent, England), fitted with an $\frac{1}{8}$ in. aperture. To find the relationship between the number of counts recorded by the camera and the film density; a point source was used to prepare Polaroid prints at different total counts. The maximum film density of the recorded radioactivity was measured as described above and plotted as a logarithm against the total number of counts. Under these conditions a linear relationship was observed up to 3,000 counts (Fig. 5). This graph was used to determine the relative difference in counts between various areas of the Phogamma pictures (Table II).

RESULTS

"In vitro"

The Williams phantom used in this series of experiments is constructed so that the ratio of radioactivity cm^{-2} of "hot spot" is twice the radioactivity of the same area of background. On scanning this phantom the "hot spots" of radius greater than 1·1 cm were discernible (Fig. 1a). Computerized processing of the scan by a nine-point smoothing technique and also by subtraction of background counts failed to improve the resolution of the "hot spots". A "hot spot":background ratio of specific activities of 2:1 would therefore appear to be the minimum requirement for visualization of the 1 cm embolus.

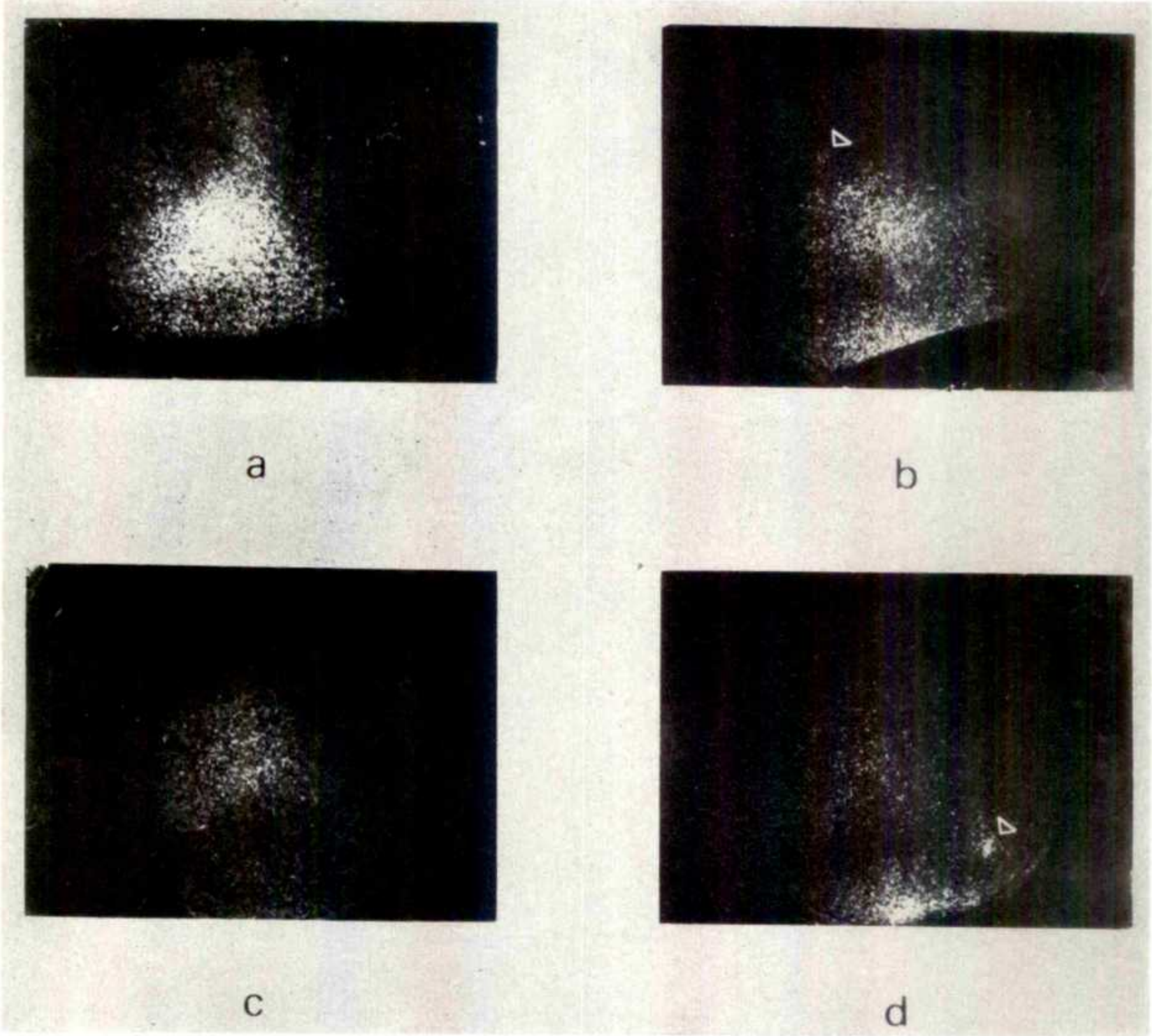

FIG. 3.
Phogamma pictures taken from the left-hand side of the heart, lung region before (a, c) and after (b, d) the reappearance of the "hot spot" in Dogs 3 and 4 respectively. The site of each "hot spot" is indicated by an arrow.

To determine the effect of superimposed background, the experiment was repeated but with the Williams phantom overlaid with another flat uniform phantom containing one-fifth of the radioactivity concentration per unit area. Under these conditions, the ratio "hot spot":background level was lowered to 1·92:1 and it was not possible to detect the 1·1 cm "hot spot"; and the 1·9 cm "hot spot" was resolved poorly (Fig. 1b). The presence of overlying lung tissue containing background activity would be expected therefore to have an appreciable effect upon the visualization of labelled emboli.

When the Phogamma gamma-camera was used in this experimental set-up, similar results were obtained.

"In vivo"

Method A. Dog 1: The first embolus was of 2 EAVE. It moved to a posterior basal segmental artery, and was not visible on scanning. A second embolus of 4 EAVE moved to a similar position to the first (Fig. 2a) and the two emboli together (total EAVE of 6) were visible on scanning from the right-hand side (Fig. 2b). A third embolus of 4 EAVE

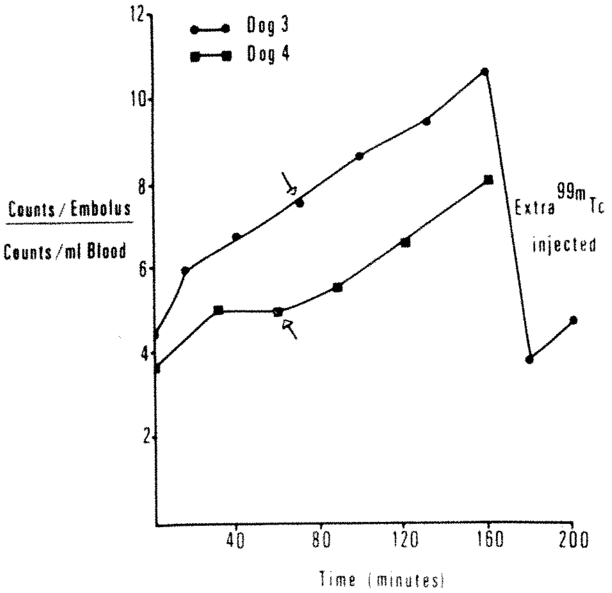

FIG. 4.

The change in EAVE (as defined in the text) during the disappearance of ^{99}Tc^{m} from the circulation. The arrows indicate the points at which the hot spot became visible.

TABLE I

THE DISTRIBUTION OF COUNTS BETWEEN EMBOLUS AND NON EMBOLUS ON PICKER SCANS

Dog no.	Area description	Total number of elements	Total counts	Counts/hot spot counts/area
1	Embolus H1	10	745	
	Lung B1	10	568	1·3
	Lung B2	10	446	1·65
	Heart B3	10	1,048	0·71
2	Embolus H1	30	4,067	
	Lung B1	30	1,800	2·2
	Lung B2	30	2,127	1·9
	Heart B3	30	3,269	1·2
	Heart B4	30	3,196	1·3

moved close to the heart and was not visible on scanning.

Dog 2: The first embolus (4 EAVE) lodged peripherally, and was not apparent on scanning. A second embolus of 16 EAVE lodged in the posterior basal segment of the left lower lobe (Fig. 2d), and was quite visible on scanning (Fig. 2e).

The total counts associated with different areas of the scan are shown in Table I. The results in Dog 1 show that where the EAVE was 6 the ratio of counts from the embolus background with respect to two separate areas of lung background were 1·3 and 1·65 respectively.

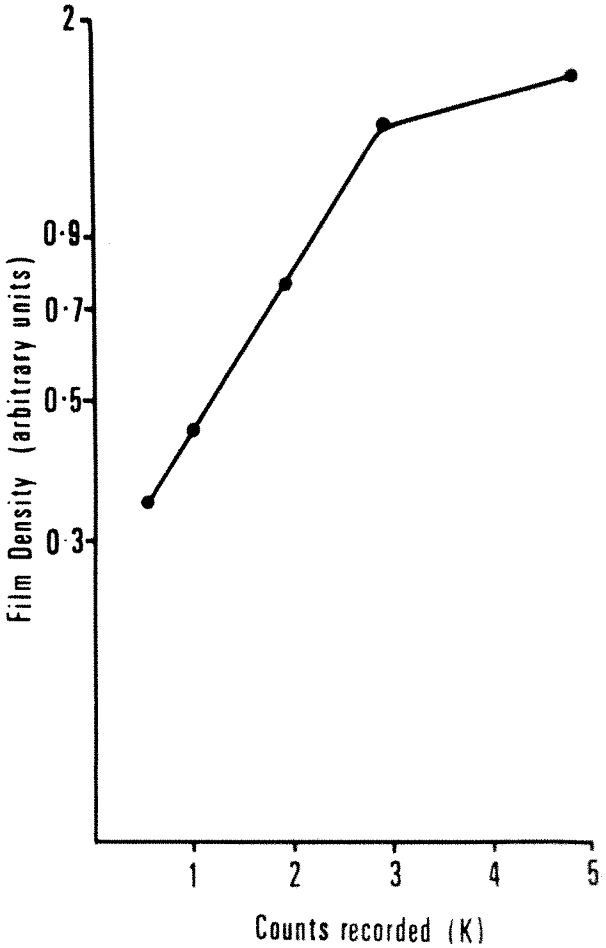

FIG. 5.

Graph relating film density on Phogamma pictures to the number of counts recorded by the Phogamma gamma-camera. (Background film density gave a reading of 0·3 units.)

In Dog 2, where the EAVE was 16, this ratio rose to 2·1:1.

Method B. Dog 3: The embolus lodged in the anterior part of the basal segment of the left lower lobe. After intravenous injection of background activity the embolus was not visible (Fig. 3a), but reappeared when the EAVE had risen to 7 (Figs. 3b and 4). On reinjection of further amounts of ^{99}Tc^{m} (Fig. 4) the EAVE dropped to 4 and the thrombus was not apparent.

Dog 4. The embolus lodged in the left posterior basal region of the lung and the embolus became

TABLE II

THE DISTRIBUTION OF COUNT DENSITY BETWEEN EMBOLUS AND NON EMBOLUS AREAS ON PHOGAMMA PHOTOGRAPHS

Photo No.	1	2	3	4	5
Embolus	2·1	2·0	2·9	1·3	1·8
Lung	1·5	1·25	—	0·9	1·15
Heart	3·0	2·5	—	1·5	2·4
Liver	—	3·0	—	3·5	—

Photo No.	Description of source
1	Dog 3: 80 minutes post injection; liver screened
2	Dog 3: 160 minutes post injection; liver unscreened
3	Dog 4: pre-injection of background; embolus only
4	Dog 4: 120 minutes post injection; liver unscreened
5	Dog 4: 160 minutes post injection; liver screened

Counts are given as arbitrary units calculated according to the method described in the text.

visible when the EAVE had reached 5 (Figs. 3c and d, Fig. 4).

The results of analysis of Polaroid prints are shown in Table II. As indicated in Table II, on two of the photographs the liver region, an area of high background, was screened by a 2 mm lead sheet in an attempt to improve the resolution of the emboli.

In Dog 3, the ratio of embolus to background recorded by the Phogamma gamma-camera was 1·45:1 when the embolus activity volume equivalent was 7·5. When the EAVE rose to 10·5 the ratio rose to 1·6:1.

In Dog 4, the embolus was sited more peripherally and at an EAVE of 6·5 the ratio of embolus to background was 1·4:1. At 160 minutes the EAVE rose to 8 and the ratio to 1·6:1.

DISCUSSION

In the first part of this study a determination was made of the effect of embolus size and activity upon its detection as a "hot spot" *in vitro*. A phantom used to represent emboli from 1·1 to 3 cm in size showed that, under ideal scanning conditions, a relative concentration of radioactivity of 2:1 was required for the detection of a 1·1 cm "hot spot" by both the Picker Magnascanner and the Phogamma gamma-camera. However, the loss of resolution apparent after superimposition of a flat phantom with one-fifth of the concentration of radioactivity indicated that such a level of relative activity might be insufficient under conditions *in vivo*.

Method A, observing ^{131}I-labelled emboli *in vivo* showed that an EAVE of at least 6 was required to obtain visualization of an embolus lying in the centre of the lung. The background radioactivity to an embolus which tends to prevent visualization will be made up of vascular and extravascular components, and only the vascular component is used in the calculation of the EAVE values. Since there will be differences between the extravascular amounts of the ^{99}Tc$^{\mathrm{m}}$ and ^{131}I-albumin it is not possible to directly compare the EAVE values of method A and B. However, the results obtained by Method B also suggested that an EAVE of at least 6 was necessary before the embolus became visible. These values will apply to emboli lying in the lung away from the heart. Higher relative concentration values would be necessary for emboli lying close to regions of high background, *i.e.* heart and liver. This consideration might be important since 50 to 60 per cent of emboli are situated basally, close to the liver background (Tow and Wagner, 1967).

From the reported results of radiopharmaceutical uptake, these results suggest that plasminogen (Gomez *et al.*, 1963), plasmin (Ouchi and Warren, 1962) and leucocytes (Kwaan and Grumet, 1972) may not be suitable for embolus detection under normal conditions but that streptokinase (Dugan *et al.*, 1973), urokinase (Rhodes *et al.*, 1972) and fibrinogen/fibrin antibody (Spar *et al.*, 1969) have sufficient affinity to be of use as thrombo-embolic scanning agents.

The result of this work should be helpful in a search for radiopharmaceuticals suitable for the detection of formed thrombi and emboli. Recent reports have been concerned with setting up screening procedures for such compounds *in vitro* (Scully *et al.*, 1973; Strachan *et al.*, 1974).

These studies have indicated a significant correlation between the observed level of uptake of a proposed radiopharmaceutical by the thrombus *in vitro* and the observed level of uptake *in vivo*. The results reported here have determined a level of activity in the embolus relative to blood background which is the minimum required to obtain visualization of embolus. This value may serve as a basis for deciding by an *in vitro* screening procedure whether a prospective radiopharmaceutical will be suitable as an embolus-detecting agent.

ACKNOWLEDGMENT

This work was supported by the Medical Research Council (Grant No. G971/34/C).

REFERENCES

DUGAN, M. A., KOZAR, J. J., GANSE, G., and CHARKES, N. D., 1973. Localisation of deep vein thrombosis using radioactive streptokinase. *Journal of Nuclear Medicine, 14,* 233–235.

GOMEZ, R. L., WHEELER, H. B., BELKO, J. S., and WARREN, R., 1963. Observations on the uptake of a radioactive fibrinolytic enzyme by intravascular clots. *Annals of Surgery, 158,* 905–911.

KWAAN, H. C., and GRUMET, G., 1972. Detection of venous thrombosis by ^{51}Cr-labelled leucocytes. *Blood, 40,* 940.

LINTON, D. S., BELLON, E. M., BODIE, J. F., and REJALI, A. M., 1971. Comparison of results of pulmonary arteriography and radioisotope lung scanning in the diagnosis of pulmonary emboli. *American Journal of Roentgenology, Radium Therapy & Nuclear Medicine, 112,* 745–748.

OUCHI, H., and WARREN, R., 1962. Detection of intravascular thrombi by means of ^{131}I-labelled plasmin. *Surgery, 51,* 42–49.

RHODES, B. A., TWAIHI, K. S., BELL, W. R., and WAGNER, H. N., 1972. Radioactive urokinase for blood clot scanning. *Journal of Nuclear Medicine, 13,* 646–648.

SCULLY, M. F., STRACHAN, C. J. L., and KAKKAR, V. V., 1973. Binding of iodinated proteins to forming and preformed thrombi. *Biochemical Society Transactions, 1,* 1204–1205.

SPAR, I. L., PERRY, J. M., BENZ, L. L., DE WEESE, J. A., MAHONEY, E. B., IZZO, M. J., SCHWARTZ, S. I., and YU, P. N., 1969. Detection of left atrial thrombi. *American Heart Journal, 78,* 731–739.

STRACHAN, C. J. L., SCULLY, M. F., and KAKKAR, V. V., 1974. The behaviour of isotope-labelled proteins in thrombosis. *Thrombosis Research, 3,* 303–318.

TOW, D. F., and WAGNER, H. N., 1967. Recovery of pulmonary arterial blood flow in patients with pulmonary embolism. *New England Journal of Medicine, 276,* 1053–1059.

Book reviews

Les radioisotopes au service du diagnostic médical. Edited by J. Ingrand and M. Hegesippe, pp. 224, 136 illus., 1975 (Paris, Masson and Cie).

This is the second edition of this French handbook of *in vivo* and *in vitro* radioisotope tests. It commences with a brief résumé on generalities, followed by chapters on each of the systems or individual organs. The text is extremely brief, concentrating on a series of headings with a few comments on each subheading: normal and abnormal values, methods, dosimetry, etc. On the other hand, virtually every method of using radioactivity for diagnosis or treatment is documented. One of the main features of the book is the liberal use of references. These are divided into several sections. For example, the bibliography on the thyroid gland covers general interest papers, pathology, reviews, special techniques and quantitative papers and books. In this section alone there are 125 references. While the text and illustrations are French in origin, the references cover the world literature.

The illustrations are not quite so good as might be expected. Many are reproductions of the older-type black and white tapper scans. Thus the book is more valuable as an *aide mémoire* for nuclear medicine specialists rather than a text-book for the student. For the specialist it will also be valuable as a useful reference book to the key papers on radioactive diagnostic methods. Naturally, being in French, its appeal will be limited. An English translation would be appreciated.

V. R. MCCREADY.

Year Book of Nuclear Medicine. 1975 edition. Edited by James L. Quinn. 90 ills., pp. 399 (Lloyd-Luke (Medical Books) Ltd), £12·50.

This *Tenth Year Book of Nuclear Medicine* appears in a new cover, but the contents follow the usual pattern.

Most readers are aware that these year-books survey the literature of the appropriate speciality. The selected papers are expertly condensed into rather long abstracts. In this volume, nuclear medicine is interpreted widely, the book covering most aspects of radioisotope, diagnostic (and occasionally physiological) applications. The abstracts are well illustrated by figures and graphs. A volume such as this is particularly useful in that the selection of articles covers more journals than one would normally encounter in the average library. Usually the abstracts are quite sufficient to give the main points of the paper without further reference to the original paper.

The *Year Book of Nuclear Medicine* is useful in that it refreshes the memory of articles already seen, brings new material to ones notice and gives a general survey of the subject. This year it makes the rather sombre point that there is no startling new development in functional studies to balance the impact which the EMI scanner will make on the imaging aspects of nuclear medicine. Nevertheless, there is a general impression of steady if less dramatic progress in the subject. This series can be thoroughly recommended for libraries, specialists and particularly those with just a passing interest.

V. R. MCCREADY

1976, *British Journal of Radiology*, *49*, 50–55

Rectilinear scanning in the detection of acute myocardial infarction

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(*Submitted May, 1975 and in revised form July, 1975*)

ABSTRACT

Myocardial scintigraphy with phosphate bone scanning agents is a new and very useful development in the detection of acute myocardial infarction. Initial experience using a rectilinear scanner is described in 50 consecutive patients admitted to hospital because of suspected myocardial infarction. The routine dose was 15 mCi/5 mg, ^{99}Tc^{m} stannous pyrophosphate intravenously with anterior, left anterior oblique, and lateral scans obtained 45–90 minutes after injection.

There was only one false negative scan in 17 patients with proven acute myocardial infarction and that was 16 days after onset. There was no proven false positive investigation in seven patients in which fresh myocardial infarction could be definitely excluded, or in a further 11 cases in which it could be excluded with reasonable confidence. Myocardial scintigraphy was considered helpful in resolving the diagnostic problem in 27 out of 29 equivocal cases.

It is concluded that myocardial scintigraphy with a rectilinear scanner is a highly accurate and safe procedure in the detection of acute myocardial infarction. The optimum scanning time is two to six days after onset of suspected infarction, when a diagnostic accuracy approaching 100 per cent can be expected.

Ideally myocardial scintigraphy should be carried out in the Coronary Care Unit with a scintillation camera and indeed such cameras are now being produced commercially for use in intensive care units, with obvious wide application in the diagnosis of myocardial infarction, pulmonary embolism, deep vein thrombosis and other conditions. However very few units of this type are available at present and indeed relatively few acute general hospitals are as yet equipped with gamma cameras, though rectilinear scanners are more widely available and can, in our opinion, make a useful contribution in the diagnosis of acute myocardial infarction.

The demonstration by Bonte and his co-workers (1974) that phosphate bone scanning agents accumulate in experimentally induced myocardial infarctions, marked a very significant advance in the development of radionuclide myocardial imaging. Hitherto most techniques had suffered from the disadvantage of presenting the infarction as a negative inactive area with the radionuclide being concentrated in normal myocardium. Myocardial scintigraphy with ^{129}Cs (Romhilt *et al.*, 1973) will not differentiate between old and recent infarcts and will miss most, if not all inferior wall lesions. The new method described by Bonte *et al.* (1974) has the advantage of positively labelling the acutely infarcted area with an efficient target/background ratio of up to 10:1.

The method is based on the observation by D'Agostina and Chigo (1970) and Shen and Jennings (1972) that calcium is incorporated with hydroxyapatite within the mitochondria of myocardial cells irreversibly damaged from coronary occlusion. In the experimentally induced myocardial infarctions in anaesthetized dogs ^{99}Tc^{m} stannous pyrophosphate clearly demonstrated the area of infarction (Bonte *et al.*, 1974) and the same workers (Parkay *et al.*, 1974) successfully applied the technique in detecting acute myocardial infarctions under clinical conditions.

While a scintillation camera is the instrument of choice, the technique can also be applied using a rectilinear scanner and the purpose of this paper is to describe our initial experience of using rectilinear scanning in the detection of acute myocardial infarction.

MATERIAL AND METHODS

The material consists of 50 successive patients who had satisfactory myocardial scans following the intravenous injection of 15 mCi/5 mg ^{99}Tc^{m} stannous pyrophosphate. Each patient was scanned 45–90 minutes after the injection using a Selo D.S.8 rectilinear scanner with a 5 in. crystal. Anterior, 45 deg. left anterior oblique and left lateral scans were obtained. Anterior and oblique scans were normalized to 100 over the body of the sternum and lateral scans over the mid dorsal vertebrae, with contrast set to 50 per cent, minimum information density of 20,000 and a scanning speed of approximately 180 cm per minute. A low energy 199-hole collimater with a focal depth of 10 cm was used for the anterior and left anterior oblique, and a collimater with a 15 cm focal length for the lateral scans.

Patients referred for bone scans can be used to develop expertise and gain experience in the technique and initially, myocardial scans were carried out on six patients having skeletal surveys for metastases. They all had negative myocardial scans and are not included in the present series.

All the patients had been admitted to Galway Regional Hospital with suspected myocardial infarction, but do not include all admissions to the Coronary Care Unit during the period under review. Seriously ill cases of acute myocardial infarction and other patients requiring continuous monitoring were not referred for investigation. The patients referred included 17 cases of unequivocal recent myocardial infarction and seven cases in which this diagnosis was not seriously considered after the initial period of observation and investigation. More than half the patients (29) had a known previous history of ischaemic heart disease with or without previously known infarctions. The series consists of 38 males and 12 females ranging in age from 25 to 82 years, with a mean of 60·8 years. Apart from the exclusion of critically ill patients, the series is unselected and can be considered a reasonably representative sample of the case material expected in routine practice in an acute general hospital.

Generally the patients were referred for investigation some days after the onset of symptoms, when it was felt that continuous monitoring was no longer required, or when the patients were being transferred from the Coronary Care Unit to a medical ward for further observation. With one exception all the investigations were carried out at least 24 hours after the onset of chest pain or other symptoms, most of the patients being scanned at two to six days after the onset, though the time from onset to scanning varied from 12 hours to 26 days with a mean of six days. During the period under review three further patients had unsatisfactory scans not considered diagnostic and have not been included in the present series. The reason for the inadequate scans in those three cases was inadequate labelling of the pyrophosphate with excess free technetium reducing the target/background ratio. One patient included in the series had an unsatisfactory scan initially but this was repeated a few days later resulting in a satisfactory investigation. Six patients with initial positive scans had repeat scans to observe progress and two patients with negative scans had repeat investigations which were then positive. Two patients had two separate admissions, some months apart with a diagnosis of fresh infarction and positive scans on each occasion.

The scans were interpreted as negative, equivocal, positive or strongly positive, with the activity in the body of the sternum used as a guide to the degree of activity. Negative cases were those in which there was no appreciable localized increased activity over background activity in the cardiac area. A localized accumulation of the isotope of apparently equal activity to the sternum was considered positive (Fig. 1), if obviously of greater activity than the sternum as strongly positive (Fig. 2) and an indefinite area of activity less than that of the sternum as equivocal (Fig. 3). As far as possible an attempt was made to avoid equivocal reports, and a conscious effort was made not to overdiagnose infarction. Where oblique and lateral scans were available the infarct was reported as anterior, posterior or inferior in location but the exact localization was considered of less importance than the confirmation of recent infarction, and the lateral scan was omitted in cases with negative anterior and oblique scans, and when the E.C.G. already indicated the site of infarction.

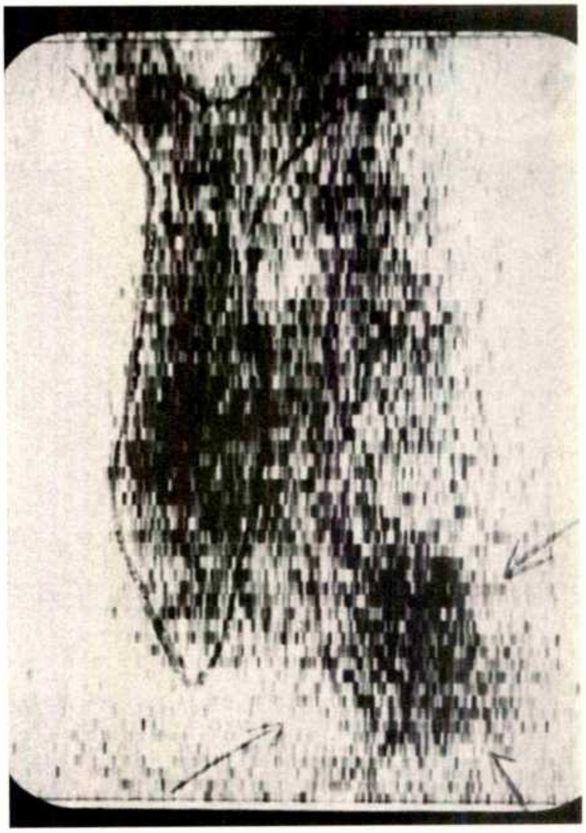
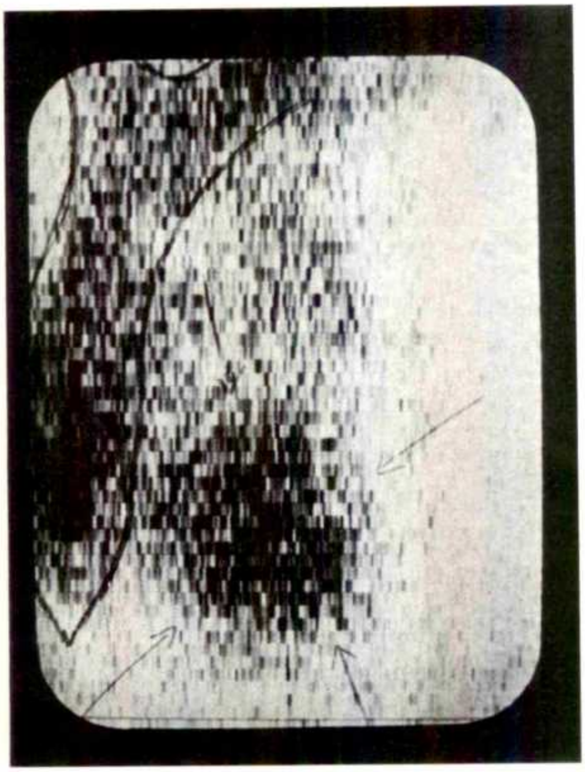


FIG. 1.
Inferior wall infarct. Positive.
Left anterior oblique scan.



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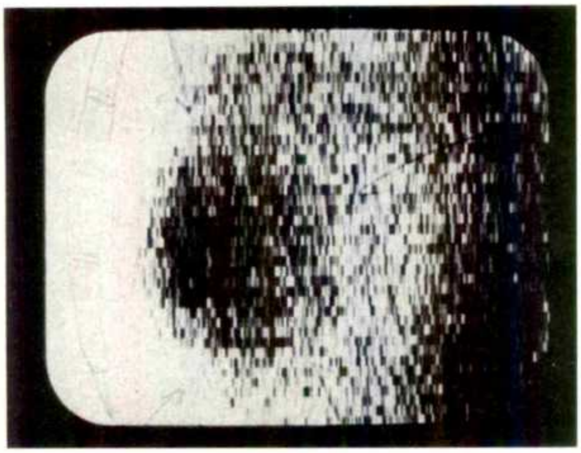

B

FIG. 2.

Antero-septal infarct. Strongly positive. (A) Left anterior oblique scan. (B) Left lateral scan.

TABLE I

POSITIVE SCANS CORRELATED WITH OTHER FINDINGS

	No. of patients
Positive scans	28
E.C.G. positive	11
E.C.G. equivocal	15
E.C.G. negative	2
Enzymes elevated	12
Final diagnosis	
(a) Recent myocardial infarct	27
(b) Doubtful recent infarction	1

TABLE II

NEGATIVE SCANS CORRELATED WITH OTHER FINDINGS

	No. of patients
Negative scans	20
E.C.G. positive	0
E.C.G. equivocal	13
E.C.G. negative	7
Enzymes elevated	1
Final diagnosis	
(a) Recent myocardial infarct	1
(b) Doubtful recent infarct	1
(c) Other diagnosis	18

RESULTS

The results are summarized in Tables I and II and correlated with the E.C.G., cardiac enzyme levels (S.G.O.T. and C.P.K.) and final diagnosis. As critically ill patients were not referred for scanning, autopsy confirmation was not available in any case, though one patient with a strongly positive myocardial scan and other indications of a recent myocardial infarction died subsequent to his discharge, apparently from a fresh infarction. The final diagnosis was the consultant physician's final assessment of each case on discharge from hospital. As myocardial scintigraphy was a new, and as yet, unproven investigation in this hospital, this assessment was made independently of the scan findings, but taking into consideration the clinical picture, physical findings and other relevant investigations and progress to final discharge from hospital.

One patient included in Table I is considered to be an example of a slowly evolving infarct. He had a negative scan 48 hours after a transient episode of anterior chest pain and at that time his E.C.G. and enzyme findings were normal. Two days after his first scan he developed severe continuous chest pain and his E.C.G. became indicative of inferior wall infarction and his enzyme levels were raised. A repeat myocardial scan four days later was strongly positive. Another patient, also included in Table I, a woman, was scanned only 12 hours after the onset

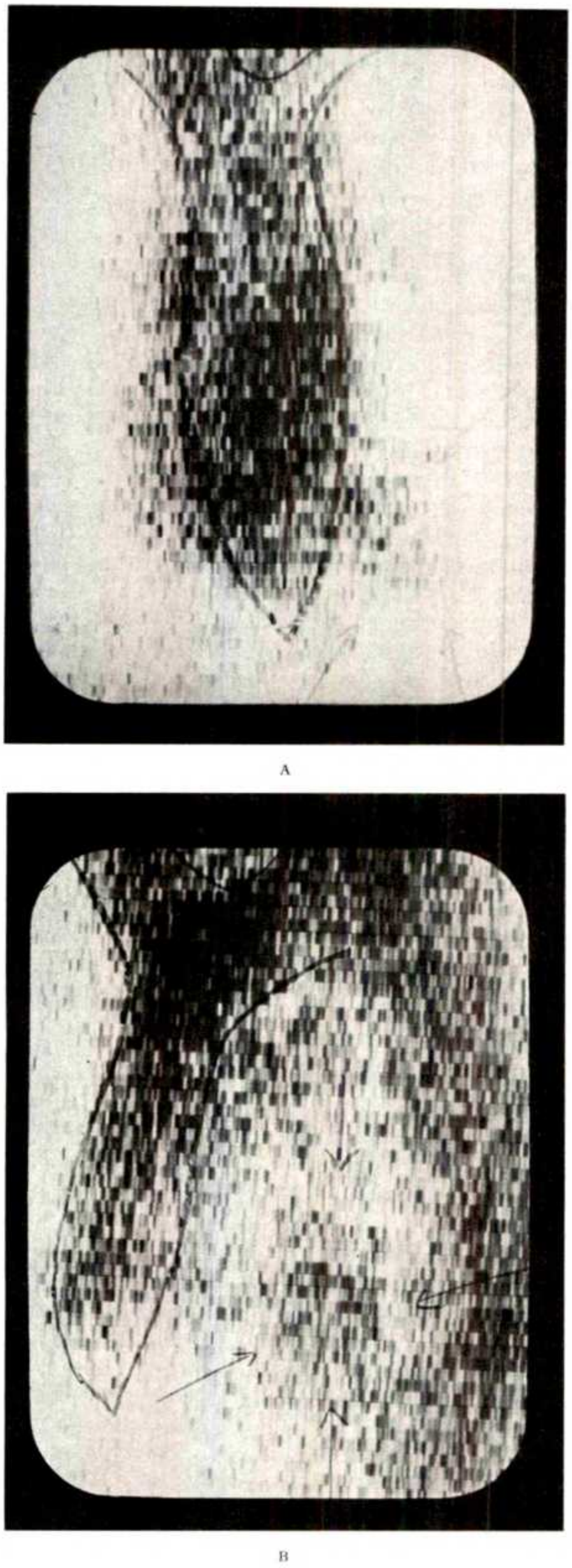

FIG. 3.
Doubtful lateral infarct. Equivocal.
(A) Anterior scan.
(B) Left anterior oblique scan.

of her chest pain, when it was negative. She had recurrence of chest pain and a repeat scan 26 days later was considered positive, when her E.C.G. changes were suggestive of antero-septal ischaemia.

The 11 patients with E.C.G. changes clearly indicating fresh myocardial infarction, all had positive scans and so had 11 out of 12 patients with elevated cardiac enzyme levels. In the single patient with a negative scan, it had been carried out 16 days after the probable onset of infarction. In all, 17 patients had clear-cut evidence of recent myocardial infarction either on E.C.G. and/or cardiac enzyme estimations, and 16 of those had positive scans, with the negative scan already referred to carried out 16 days after the infarction. One other patient with a negative scan 15 days after the onset of chest pain had a doubtful posterior wall infarction. The patient, a known hypertensive of long standing, was admitted in left ventricular failure, with E.C.G. tracings indicating left ventricular hypertrophy and strain, with a doubtful posterior wall infarct.

Eleven patients had strongly positive scans and eight of those showed undoubted evidence of fresh myocardial infarction, with this diagnosis being probable, though not proven by other means, in the other three patients. In this group the interval from infarction to scanning varied from two to 18 days with a mean of 4·7 days, with the interval exceeding six days in only one case. Repeat myocardial scans were negative at 22, 26 and 51 days after infarction in three patients having initial positive scans and less positive in three patients at 13, 14, and 17 days after infarction. Two patients had two separate admissions with undoubted fresh infarctions and on each occasion the myocardial scan was positive, at times varying from six to 21 days after the probable date of infarction.

In the present series there was only one proven false negative and that patient had been scanned 16 days after the probable time of infarction. Recent myocardial infarction could be excluded with certainty in seven patients and they all had negative scans at times varying from one to seven days (mean 2·7) after onset of symptoms. In a further 11 patients with negative scans, recent infarction could also be excluded but with a lesser degree of confidence. There was a known history of previous ischaemic heart disease in 29 patients and the scans were positive in 16, negative in 11 and equivocal in two of these cases.

Discussion

Although the present series inevitably includes a number of cases in which fresh myocardial infarction could not be confirmed or excluded with certainty, the only proven false negative scans were in a patient investigated 16 days after the onset of infarction, and in a patient with a slowly evolving infarction in which the scan was subsequently positive. None of the positive scans were proven false by other means. In addition to the high diagnostic accuracy there was an acceptably low incidence of equivocal or unsatisfactory investigations, *i.e.*, two equivocal and four unsatisfactory scans out of a total of 64 investigations.

Our experience suggests that the investigation is most useful and informative two to six days after infarction, but equivocal or false negative investigations may be expected ten or more days post-infarction. This is in agreement with the findings and conclusions of Bonte and his co-workers (1974), based on their experimental and clinical experience.

The dosage used, 15 mCi/5 mg ^{99}Tc^{m} stannous pyrophosphate, is considered a safe and effective dose by Parkay *et al.* (1974). It corresponds to 0·2 mCi/0·07 mg/kg in a patient of average weight, which is considerably below the dose of 0·25 mg/kg of pyrophosphate shown by Fletcher and his co-workers (1973) to have no effect on serum calcium or phosphorus levels. Although our patients were not monitored after injection, there was no indication that this dosage induced any cardiac arrythmias. Pyrophosphate is known to chelate calcium, with the possibility of causing hypocalcaemia, but according to the work of Stevenson and Dunson (1973) E.C.G. changes in healthy dogs were not observed until a minimum dose of 20 mg/kg was administered. Our dosage would correspond to 0·07 mg/kg in a patient of average weight, indicating a safety factor of almost 300. It has been shown that little or no blood pool activity is left in the heart at one hour (Krishnamurthy *et al.*, 1975) and we feel that the optimum scanning time is 45–90 minutes after injection. The unsatisfactory investigations were due to excess cardiac blood pool and background activity, apparently due to free unlabelled technetium, as none of those cases had any indication of impaired renal function which might have prevented clearance of pyrophosphate by the kidneys.

In all such cases undue activity in the fundus of the stomach, due to gastric excretion of technetium was apparent. We have not used any of the other phosphate bone scanning agents but have no reason to expect that they would not be safe and effective. It has been shown experimentally that pyrophosphate provides the best ratio of infarct to normal myocardium 24 hours after infarction and one hour after administration (Bonte *et al.*, 1975).

Apart from inadequate labelling or delayed blood clearance, other possible causes of error would include healing rib fractures, especially if the patient has had external cardiac massage, reflux of free technetium from the stomach into the oesophagus due to hiatal hernia which could easily occur during the left oblique and left lateral scans, or accumulation of technetium in a neoplastic or actively secreting breast. It is also likely that pericarditis can result in a positive scan persisting for a long time, if not indefinitely. Parkay *et al.* (1974) record such a case with a follow-up scintigram showing increased activity on the 17th day, and they also mention the possibility of infiltrative myocardial diseases producing positive scans.

Myocardial scintigraphy using a rectilinear scanner has got obvious limitations and cannot be used in acutely ill patients requiring continuous monitoring and the immediate availability of recuscitative measures. Recent or fresh myocardial infarction can be notoriously difficult to diagnose with reasonable certainty in cases of long standing ischaemic or hypertensive heart disease with or without known previous episodes of myocardial infarction, and the present series included 29 such cases. Myocardial scintigraphy was positive in 16, negative in 11 and equivocal in two of those cases, and so could be considered to contribute significantly to the diagnosis in 27 out of 29 cases, *i.e.* 93 per cent. It is also well known that subendocardial infarction may show a normal E.C.G., but the myocardial scan should be positive up to ten days after infarction, even after the cardiac enzymes have returned to normal. Two of our cases would fit in this category with positive scans at six and ten days post-infarction, when the cardiac enzymes, though raised initially, had returned to normal.

The experimental findings and conclusions of Shen and Jennings (1972) in respect of the kinetics of calcium accumulation in myocardial infarction are pertinent to understanding the mechanism of myocardial scintigraphy with phosphate bone scanning agents. They observed that following permanent occlusion of a coronary artery, there was no uptake of calcium in the infarcted tissue, but that calcium uptake is a feature of irreversible cellular injury only when arterial blood is present, and that it is an active process associated with mitochondrial accumulation. Calcium accumulation is not found if the cellular damage caused by ischaemia is reversible. The phosphate bone imaging agents are incorporated into the calcium phosphate granules, believed to be hydroxyapatite, within the mitochondria of the cells irreversibly damaged, and this is an active process dependant on arterial reperfusion of the infarcted area. Consequently the pyrophosphate will not be taken up in the myocardium unless there is permanent cell damage, and transient episodes of ischaemia without irreversible cell damage will not result in positive scans.

A rectilinear scanner has inherent limitations in the precise localization and delineation of infarcts as compared with a scintillation camera. While it is easy to determine if the infarct is anterior, posterior, lateral or inferior in location, it is generally too poorly delineated to determine its exact size and extent, and this imposes an obvious limitation in attempting to assess changes in extent of the infarcted area on repeat investigations, though changes in the degree of activity in the infarction can be appreciated and can be helpful in assessing progress. If extension of the infarct is suspected, increase in the accumulation of the radionuclide on serial investigations is useful confirmatory evidence.

In conclusion we feel that, despite its limitations, imaging of acute or suspected acute myocardial infarction with a rectilinear scanner, using a phosphate radionuclide is a very useful and safe procedure, especially in the patient with long standing heart disease in which the E.C.G., and other investigations may be equivocal. It can be expected to help resolve the diagnostic problem in over 90 per cent of such equivocal cases, and because of its atraumatic non-invasive nature, it is also a worthwhile investigation even in the clearcut case. It can have an accuracy approaching 100 per cent if carried out two to six days after suspected infarction. It is also useful in observing progress in the established case, and negative investigations, in conjunction with other negative or equivocal procedures can help in reducing bed occupancy by reducing the number of patients requiring prolonged observation in hospital.

SUMMARY

Myocardial scintigraphy with phosphate bone scanning agents is a new and very useful development in the detection of acute myocardial infarction. Initial experience using a rectilinear scanner is described in 50 consecutive patients admitted to hospital because of suspected myocardial infarction. The routine dose was 15 mCi/5 mg $^{99}\text{Tc}^{m}$ stannous pyrophosphate intravenously with anterior, left anterior oblique, and lateral scans obtained 45–90 minutes after injection.

There was only one false negative scan in 17 patients with proven acute myocardial infarction and that was 16 days after onset. There was no proven false positive investigation in seven patients in which fresh myocardial infarction could be definitely excluded, or in a further 11 cases in which it could be excluded with reasonable confidence. Myocardial scintigraphy was considered helpful in resolving the diagnostic problem in 27 out of 29 equivocal cases.

It is concluded that myocardial scintigraphy with a rectilinear scanner is a highly accurate and safe procedure in the detection of acute myocardial infarction. The optimum scanning time is two to six days after onset of suspected infarction, when a diagnostic accuracy approaching 100 per cent can be expected.

ACKNOWLEDGMENTS

We thank Professor James L. Quinn, III, Northwestern Memorial Hospital, Chicago, who introduced the method to us, and advised on the technique. We also thank the Consultant Physicians of Galway Regional Hospital who made their case notes freely available for this study.

REFERENCES

BONTE, F. J., PARKAY, R. W., GRAHAM, K. D., MOORE, J., and STOKELY, E. M., 1974. A new method for radionuclide imaging of myocardial infarcts. *Radiology*, *110*, 473–474.

BONTE, F. J., PARKAY, R. W., GRAHAM, K. D., and MOORE, J. G., 1975. Distributions of several agents useful in imaging myocardial infarcts. *Journal of Nuclear Medicine*, *16*, 132–135.

D'AGOSTINA, A. N., and CHIGA, M., 1970. Mitochondrial mineralisation in human myocardium. *American Journal of Clinical Pathology*, *53*, 820–824.

FLETCHER, J. W., SOLARIC-GEORGE, E., HENRY, R. E., and DONATI, R. M., 1973. Evaluation of ^{99m}Tc-Pyrophosphate as a bone imaging agent. *Radiology*, *109*, 467–469.

KRISHNAMURTHY, G. T., HUEBOTTER, R. J., WALSH, C. F., TAYLOR, J. R., KEHR, M. D., TUBIS, M., and BLAHD, W. H., 1975. Kinetics of ^{99}Tc-labelled Pyrophosphate and Polyphosphate in Man. *Journal of Nuclear Medicine*, *16*, 109–115.,

PARKAY, R. W., BONTE, F. J., MEYER, S. L., ATKINS, J. M., CURRY, G. L. STOKELY, E. M., and WILLERSON, S. T., 1974. A new method for radionuclide imaging of acute myocardial infarction in humans. *Circulation*, *50*, 540–546.

ROMHILT, D. W., ADOLPH, R. J., SODD, V. J., LEVENSON, N. J., AUGUST, L. S., NISHIYAMA, H., and BERKE, R. A., 1973. Cesium-129 Myocardial Scintigraphy to detect myocardial infarction. *Circulation*, *48*, 1242–1251.

SHEN, A. C., and JENNINGS, R. B., 1972. Kinetics of calcium accumulation in acute myocardial ischaemic injury. *American Journal of Pathology*, *67*, 441–452.

STEVENSON, J. S., and DUNSON, G. L., 1973. Cardiac changes with ^{99m}Tc-Tin-Phosphate Radiopharmaceuticals. *Journal of Nuclear Medicine*, *14*, 774.

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1976, *British Journal of Radiology*, *49*, 56–61

Intestinal cell proliferation during fractionated abdominal irradiation

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(*Received January, 1975 and in revised form July, 1975*)

Abstract

In the mouse, at normal steady state of cell proliferation, the compensatory proliferative response to intestinal irradiation is such that when radiation exposures totalling 1,000 R are concentrated over the first few days of the week, summated proliferative activity for the entire week is near control levels. Symmetrically distributed exposures over a five-day treatment week (200 R daily, and especially 333 R on Monday, Wednesday and Friday) result in depressed levels of overall weekly proliferation. In these instances, the weekend break is particularly crucial. Similar results were obtained when the one-week measurement period was inserted between the third and fifth week of abdominal therapy, except in this instance, 200 R per day did not result in sub-control levels of proliferation, whereas 333 R on M, W and F, continued to do so. The intestine seems able to maintain its barrier epithelium for extended periods of diminished cell input, provided such is not too severe and that it stems from decreased cell production rate per crypt rather than from crypt attrition. A partial explanation for this relative tolerance is given by the finding that the vast majority of proliferative cells, even those irradiated and rendered permanently incapable of further division, succeed in migrating up the villus and hence help to maintain a barrier epithelium. In that sense, nearly all cell divisions become useful, even in the face of repeated exposures.

In a previous report (Hagemann and Concannon, 1975), we presented a model describing the acute proliferative and compartmental response of the mouse intestine to treatments with cytotoxic agents. One aspect considered was the role of compensatory hyperplasia in the composite response of the intestinal mucosa to fractionated radiation exposure (see also Hagemann and Lesher, 1971, 1973; Hagemann, Sigdestad and Lesher, 1972). We suggested that if deviation from standard abdominal therapy (*ca.* 200 R/day; 5 day/week) be instituted, specifically fewer fractions for the same total weekly dose, one might consider concentrating the exposures over a relatively short time interval, thereby allowing ample time for the compensatory hyperplastic response to occur. The proviso was given that any single exposure set should not be severe enough to cause crypt attrition, *i.e.*, to result in less than one surviving CPC (crypt progenitor cell) per crypt.

In the present study, total cell proliferation over a one-week interval has been determined, during which abdominal irradiation was carried out with a number of fractionation schedules to a total exposure of 1,000 R. The one-week interval of measurement was either the first or the fourth week of therapy. In addition, the fate of proliferative cells in maximally hyperplastic crypts (due to prior irradiation), following another exposure, was examined.

Materials and Methods

Adult male Ha/ICR mice were used throughout. Physical factors of X-irradiation were: 270 kVcp, 20 mA, HVL 1·8 mm Cu, and a target to midline distance of 70 cm. The exposure rate, measured in air, was 68 R/minute. The animals were restrained in individual leucite holders during exposure, with adequate openings for ventilation. The portion of the mouse anterior to the zyphoid, as well as both femurs and tail, was shielded with 0·5 cm of lead. Exposure under the shielding was negligible. The following treatment schedules were used:

(1) 1,000 R single exposure on Monday (M);
(2) 333 R given three times on M, with a four-hour interval between exposures (to allow for substantial repair of sublethal damage—Withers and Elkind, 1969; Hagemann, Sigdestad and Lesher, 1971a);
(3) 250 R given twice (with a four-hour repair interval) on both M and Tu;
(4) 333 R on M, Tu, and W;
(5) 200 R on M, Tu, W, Th, F;
(6) 333 R on M, W, F.

Exposure patterns C, D, E and F were also examined during the fourth week of a therapy course.

At 12 or 24 hour intervals after irradiation, which began on Monday morning, 50 μCi tritiated thymidine were injected intraperitoneally into eight animals in each group. The animals were sacrificed 30 minutes after injection and disintegrations per minute (dpm) /mg wet weight of jejunum was measured (Hagemann, Sigdestad and Lesher, 1970). These values are directly related to the number of cells in the DNA synthetic phase of the cell cycle provided that dpm/S phase cell remains constant. The latter does not strictly obtain following irradiation due to an early transient depression in DNA synthesis (Hagemann and Lesher, 1971), along with a subsequent shortening in S phase duration

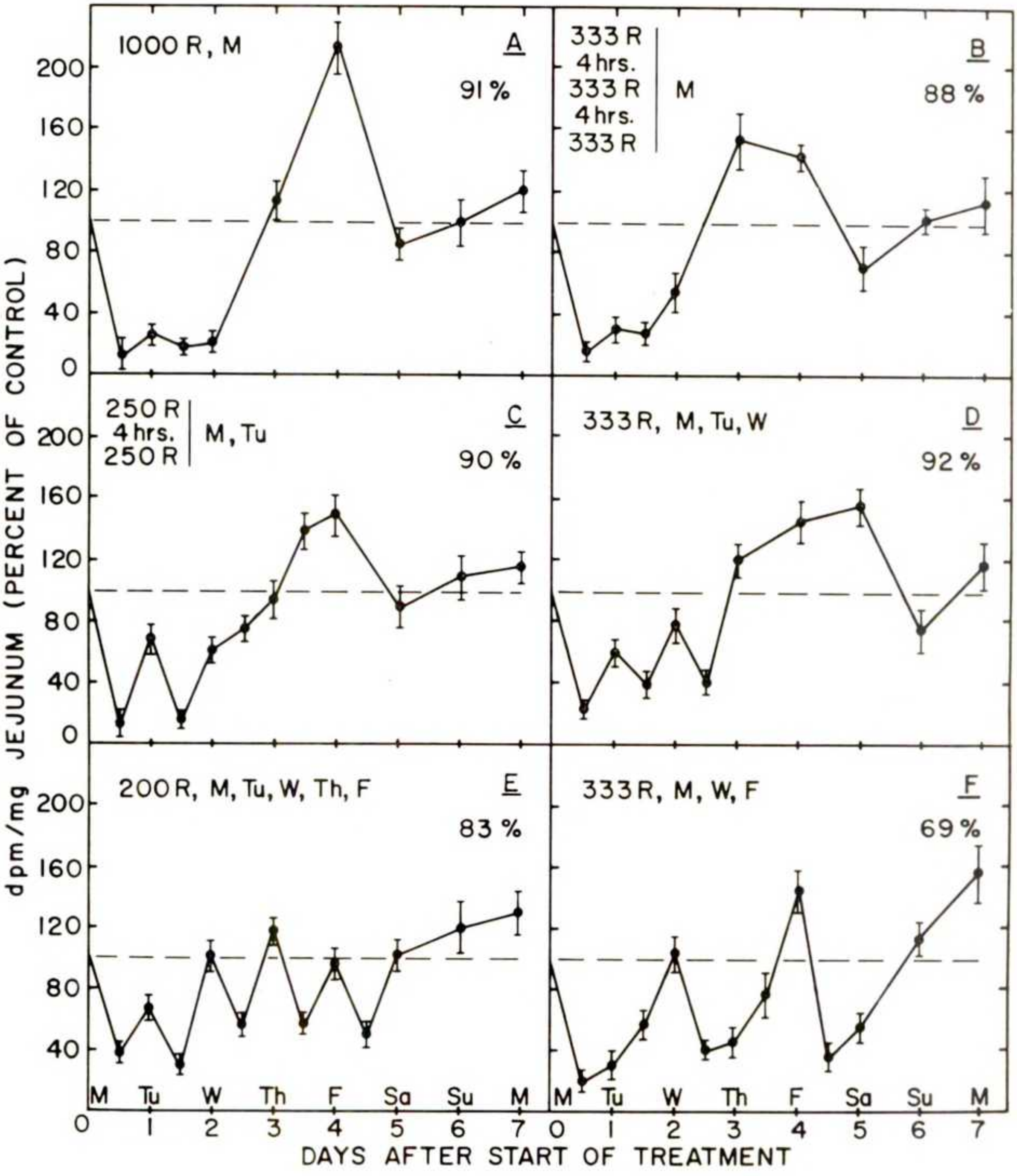

FIG. 1.

Disintegrations per minute (dpm) per mg wet weight jejunum (an estimate of proliferative activity) as a function of time after start of treatment on Monday (M). Tritiated thymidine was injected at the times shown and the animals were sacrificed 30 minutes thereafter. The exposure pattern is shown on each panel. The percentages indicate total weekly proliferation, in percent of control values (*i.e.*, the area under the experimental curves divided by the area under the control curve—dashed lines). Each point represents the mean ± SE for eight animals.

(in which the genome is yet replicated). Thus, dpm/mg approximates S phase cellularity of the tissue. S phase cellularity is related to total proliferative cellularity in general terms, but again not exactly following irradiation. This is due to some change in the relative proportion of the total cell cycle spent in the S phase, and transient alteration in population kinetics (*i.e.*, from steady state to exponential growth). Within these constraints, the data obtained provide relative estimates of the proliferative activity of the intestinal mucosa following radiation exposure; the principal point of interest is differences between the various exposure patterns rather than the absolute numbers involved.

It became important to know the fate of the cells which were highly proliferative due to previous radiation exposure(s), and were then exposed to a subsequent treatment. If they were to die and disintegrate *in situ* they would be of no use to the animal; whereas if they ascended the villus, they could serve a barrier function. Six animals were irradiated abdomen only with 1,000 R. Four days later, a time at which the crypts are maximally proliferative and composed entirely of actively dividing cells, 50 μCi ^{3}HTdR were injected, and 20 minutes later the animals were irradiated with 800 R. At 12 and 24 hours after this exposure, three animals were sacrificed. Control animals received no irradiation. Segments of jejunum were prepared for radioautography using standard histological techniques, and the location of labelled nuclei was ascertained.

Results

The data obtained for the first week of irradiation are shown in Fig. 1. Disintegrations per minute per mg as a percentage of the control value (an approximate indicator of total proliferative activity) is plotted as a function of time after the onset of treatment. Each panel represents a different fractionation scheme (as shown) employed to deliver a total of 1,000 R in one week. The percentage indicated on each panel represents total proliferative activity relative to the control level, during the seven-day period. These values were obtained by dividing the area under each curve by the area under the control curves (represented by the dashed line).

Panel A shows the proliferative response to a single exposure of 1,000 R given on Monday. It is similar to previously published curves (Hagemann and Lesher, 1971) and exhibits initial depression (part of which, in the first 24–36 hours, is due to a transient depression in DNA synthesis per S phase cell), followed by a compensatory overshoot in proliferative activity and subsequent reinstatement of homeokinetic control. Interestingly, the compensatory response is such that total proliferative activity, when integrated over the seven-day span, is near that of control animals. In Panel B, the 1,000 R was delivered also in one day, but with four hours between successive 333 R exposures. Therefore, the total degree of damage inflicted was less than for 1,000 R single doses (due to repair of sublethal injury). This is because each exposure kills fewer CPC due to the pronounced shoulder on the CPC survival curve (Withers and Elkind, 1969; Hagemann, Sigdestad and Lesher, 1971b) coupled wih the intromission of time intervals for repair of sublethal radiation damage (Withers and Elkind, 1969; Hagemann, Sigdestad and Lesher, 1971a). We have shown previously (Hagemann and Lesher, 1973) that up to the point of causing crypt attrition, the magnitude of the total compensatory response is directly related to the amount of damage inflicted (*i.e.*, to radiation dose). When compared with Panel A, it may be seen that the compensatory response is somewhat less in Panel B; the degree of damage is also less because of repair between successive fractions. Nevertheless, the total proliferative activity over the one-week interval is near that of the control.

Panel C illustrates the effect of two exposures of 250 R, separated by four hours, given on both Monday and Tuesday. Damage is less, due to the shoulder on the CPC survival curve, allowance for repair of sublethal damage, and provision of time for proliferation between exposure sets. The compensatory proliferative response is again diminished. (The effectiveness of the proliferative activity which occurred between exposure sets in this and remaining régimes provided the rationale for ascertaining the fate of these cells following a subsequent exposure; see later.) Summated proliferative activity for this fractionation schedule is 90 per cent of control.

In Panel D, 333 R was given on the first three days of the week. Cell killing combined with a period of greatly decreased cell input into the villous compartment results in a substantial compensatory proliferative response. Since the last exposure is completed five days before the following Monday, sufficient time is provided for attainment of the complete response, and overall proliferative activity for the week is similar to that of the control.

Panel E illustrates the usual pattern of exposure employed clinically. During the course of the week, proliferative activity progresses from about 40 per cent of control to somewhat above the control level (this largely because of the Friday–Monday radiation free interval; see Hagemann and Concannon (1975) for a discussion of this point). For the entire

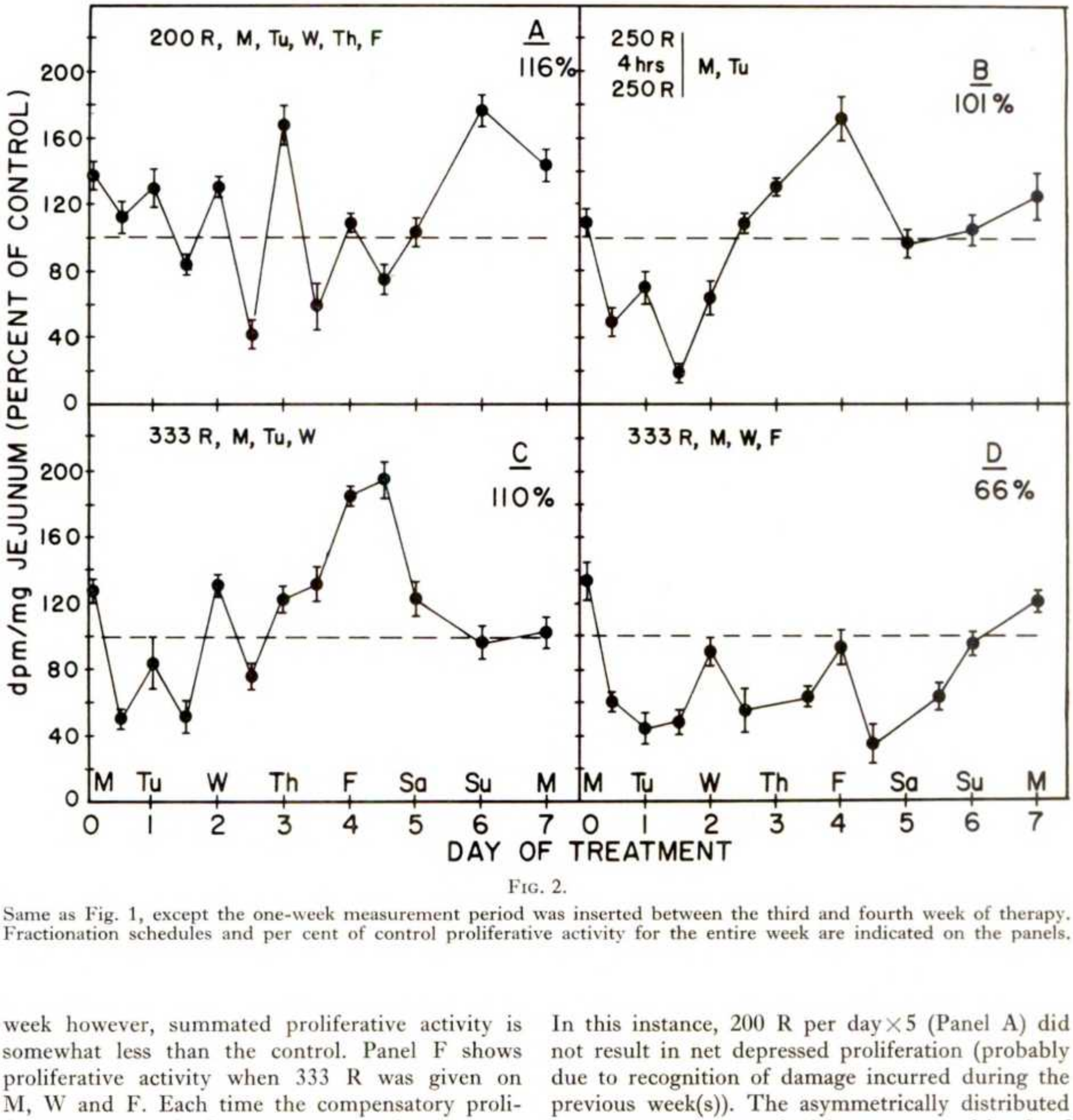

FIG. 2.

Same as Fig. 1, except the one-week measurement period was inserted between the third and fourth week of therapy. Fractionation schedules and per cent of control proliferative activity for the entire week are indicated on the panels.

week however, summated proliferative activity is somewhat less than the control. Panel F shows proliferative activity when 333 R was given on M, W and F. Each time the compensatory proliferative response is about to occur, another exposure is given and, over the course of the week, total proliferative activity is markedly compromised. Substantial gain is seen over the weekend, which is probably critical for this regimen to be employed with success. Again, it became vital to know whether the spikes of proliferative activity seen on W, F and Su result in proliferating cells, which, even though to be irradiated again, can ascend the villus.

Four of the exposure patterns described above were tested in a similar fashion during the fourth week of therapy. The results are shown in Fig. 2. In this instance, 200 R per day×5 (Panel A) did not result in net depressed proliferation (probably due to recognition of damage incurred during the previous week(s)). The asymmetrically distributed exposure patterns resulted in near control levels of integrated proliferative activity (Panels B and C). Exposures of 333 R given on M, W and F (Panel D) again resulted in a substantial reduction in net cell production. In addition, animal lethality began to accrue in this group during the fourth week; 33 per cent of the animals had died (probably from intestinal damage) by the end of the period.

To examine the fate of maximally proliferative crypt cells when exposed to a succeeding dose of radiation, animals were irradiated with 1,000 R. Four days later, when the surviving crypts were

TABLE I

MIGRATION OF LABELLED CELLS FROM CRYPTS OF CONTROL AND IRRADIATED (800 R) ANIMALS AT 12 AND 24 HOURS AFTER PULSE LABELLING WITH TRITIATED THYMIDINE

	Control		Irradiated	
	12 hours	24 hours	12 hours	24 hours
Location of uppermost labelled cell*	9·7	46·0	15·9	55·6
Number of labelled cells per villus†	12·4	56·7	22·0	76·1

*Cell positions from top of crypt.
†Two-dimensional measure from tissue sections.

maximally hyperplastic, they received ^{3}HTdR and, 20 minutes thereafter, 800 R. The results are shown in Table I. After irradiation, labelled nuclei populate the villi at near the control rate. Clearly, these highly proliferative cells, although the vast majority were lethally damaged with respect to reproductive integrity, nevertheless differentiated morphologically. Presumably, they can perform at least a barrier function and hence delay villous cell depletion and mucosal denudation.

DISCUSSION

The data illustrate that the mode of radiation fractionation can profoundly influence intestinal proliferative activity integrated over a one-week interval. In general, exposures delivered over a relatively short period, *e.g.* 1–3 days, cause substantial damage which elicits, over the next 4–6 days, a marked compensatory proliferative reaction such that total proliferative activity for the entire week is near to that of control. It has been shown (Lesher, 1967) that, during the compensatory response to irradiation, the S phase may comprise as much as 70–75 per cent of the cell cycle, as opposed to the steady state value of 60 per cent. This would suggest that the actual integrated cell proliferation in Panels A–D (Fig. 1) and B–C (Fig. 2) is 10–15 per cent lower than indicated by the activity data.

However, the rate of DNA synthesis per S phase cell is slowed for the first 12–24 hours after exposure (Hagemann and Lesher,* 1971), which leads to some underestimation of the proliferative activity. Thus, the dpm/mg values shown on the figures are probably reasonable estimates of integrated proliferative activity. Fractionation patterns symmetrically imposed over a five-day exposure week do not allow the potential compensatory response to occur in the interval between exposures, and, as a result, proliferative activity integrated over the week is compromised. In the latter cases, instillation of a weekend recovery period is probably crucial (see also Hagemann and Concannon, 1975). In the case of 200 R per day, the total unrecovered damage incurred during the first week of therapy is probably insufficient to elicit a maximal compensatory response; and net cell production, while below control levels, is not yet recognized (in the proliferation control sense) as threatening. As this treatment continues into the fourth week, however, damage recognition is present, accelerated proliferation is instituted, and net cell production is compensatorily maintained at, or somewhat above, the control level. Note that the weekend recovery period contributes significantly to the summed cell production. Exposures of 333 R on M, W and F cause sufficient damage even in the first week to elicit a compensatory hyperplastic response. However, this is largely thwarted by successive exposures just as the response commences. The situation is maintained into the fourth week of therapy and net cell production is severely compromised. At the end of this period (4,000 R in four weeks), animal lethality amounted to 33 per cent, which is in line with our previous finding of 50 per cent lethality with 5,300 R given as 300 R fractions on M, W and F (Hagemann and Concannon, 1975).

It is of interest to assimilate the present findings with those previously published on animal survival following multifraction abdomen-only irradiation (Hagemann and Concannon, 1975). An exposure of 1,000 R given once per week, although resulting in control levels of proliferative activity over the first week, (Fig. 1, Panel A) results in crypt killing which is progressive with each exposure, and relatively few exposures can be accumulated. Smaller exposure fractions, separated by several hours, can be repeated many times provided:

(1) a given set of irradiations does not cause crypt attrition; and
(2) sufficient time is provided between sets for the compensatory proliferative response to come into play (Fig. 1, Panels B and C; Fig. 2, Panel B).

These considerations would also apply to exposures concentrated in the early part of the week. Following 200 R/day, 5 days/week, cell proliferation is decreased somewhat during the first week (Panel E), yet large total exposures (over 10,000 R) can be accumulated. As is apparent from Fig. 2 (Panel A), that during the course of four weeks' treatment, cell proliferation accelerates to the control level or slightly above. Even following 300 R/day, given on

M, W and F, animals survive more than 5,000 R, although this temporal regimen substantially decreases summated proliferative activity (Fig. 1, Panel F; Fig. 2, Panel D). (In the present study, 67 per cent of the animals survived 4,000 R given as 333 R on M, W and F.) Thus, it would appear that:

(1) the intestinal epithelium is capable of maintaining an intact barrier epithelium in the face of diminished net cell production for a time, provided the decrease is not too severe and that it stems from reduced cell production rate per crypt and not from crypt attrition;

(2) cells in the proliferative compartment, either at steady state (Hagemann and Lesher, 1973) or dividing at a greatly accelerated rate (present study), which are rendered incapable of sustained division by irradiation, nevertheless retain the capacity to migrate up the side of the villus, perform at least a barrier function, and provide a temporal extension for the concurrent proliferative events in the crypt to provide subsequent restorative cell input into the villous compartment.

Returning to Figs. 1 and 2, we note that, for exposures concentrated over the first few days of the week, the compensatory response is essentially completed about two days prior to the next scheduled Monday irradiation. Thus, during this time interval the intestinal epithelium is near steady state with respect to cell production, while a (presumptive) surviving tumour cell population would be increasing in number. Would either commencing the next course of radiotherapy at the completion of the compensatory hyperplastic response, or the institution of selected chemotherapy during this interval, improve the therapeutic ratio? The latter course would seem particularly attractive if intestinal tolerance to moderate radiotherapy is dictated by delayed manifestations of radiation damage to slowly proliferating supportive tissues (which may not be appreciably affected by cycle specific agents), rather than by eventual failure of the principal cell renewal system (see Hagemann and Concannon, 1975). These possibilities are currently under investigation.

ACKNOWLEDGMENT

We thank Miss G. Thomas for skilled and dedicated technical assistance. This study was supported by USAEC contract AT(11-1)-3098 and by grants No. 1PO2CA10438-03 and 5TO1CA05224-03 from the National Cancer Institute.

REFERENCES

HAGEMANN, R. F., and CONCANNON, J. P., 1975. Time/dose relationships in abdominal irradiation: A definition of principles and experimental evaluation. *British Journal of Radiology*, *48*, 545-555.

HAGEMANN, R. F., and LESHER, S., 1971. Irradiation of the G.I. tract: compensatory response of stomach, jejunum and colon. *British Journal of Radiology*, *44*, 599-602.

1973. Intestinal cytodynamics: Adductions from drug and radiation studies. In *Drugs and the Cell Cycle*, edited by Zimmerman, Padilla and Cameron, pp. 195-217 (Academic Press, New York).

HAGEMANN, R. F., SIGDESTAD, C. P., and LESHER, S., 1970. A method for quantitation of proliferative intestinal mucosal cells on a weight basis: some values for C57Bl/6 *Cell and Tissue Kinetics*, *3*, 21-26.

1971a. Intestinal crypt survival and total and per crypt levels of proliferative cellularity following irradiation: Fractionated X-ray exposures. *Radiation Research*, *47*, 149-158.

1971b. Intestinal crypt survival and total and per crypt levels of proliferative cellularity following irradiation: Single X-ray exposures. *Radiation Research*, *46*, 533-546.

1972. Intestinal crypt survival and total and per crypt levels of proliferative cellularity following irradiation: Role of crypt cellularity. *Radiation Research*, *50*, 583-591.

LESHER, S., 1967. Compensatory reactions in intestinal crypt cells after 300 roentgens of cobalt-60 gamma irradiation. *Radiation Research*, *32*, 510-519.

WITHERS, H. R., and ELKIND, M. M., 1969. Radiosensitivity and fractionation response of crypt cells of mouse jejunum *Radiation Research*, *38*, 598-613.

1976, *British Journal of Radiology*, *49*, 62–70

A practical approach to transverse-section gamma-ray imaging

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(*Received August, 1974 and in revised form May, 1975*)

Abstract

The object of transverse-section γ-ray imaging is to display the concentration of radioactive material in a thin transverse slice of the body. The technique is essentially that of reconstructing a density distribution from its projections, and many methods have been developed to perform the reconstruction.

This report describes the realization of three such methods, using a small digital computer PDP8 I, and their application to experimental and clinical data obtained from the Aberdeen Section Scanner:
(1) simple back projection;
(2) the convolution method of Bracewell and Riddle;
(3) the linear integral transform method of Radon.

The problems of sensitivity variation and attenuation are examined. An approximate attenuation correction procedure is described. The reconstruction method of Bracewell and Riddle was found convenient since then the data were manipulated in a manner where smoothing to reduce statistical noise and correction for absorption could both be readily incorporated.

Transverse-section radioisotope tomography introduced by Kuhl and Edwards (1964) has proved valuable in routine clinical brain-scanning investigations. The object of this procedure is to display the concentration of radioactive material in a thin transverse slice of the body. The section image is not achieved by blurring the images of adjacent planes, as in conventional X-ray tomography, but rather the plane of the section is limited entirely by collimation, the method also chosen for the recently introduced EMI scanner (Hounsfield, 1973). The technique is essentially that of reconstructing an object or density distribution from its projections. Reconstruction methods, varying in accuracy and complexity, have been developed in diverse fields including radio-astronomy, electron microscopy and radiology, and these methods are currently being applied to transverse section γ-ray imaging. The object of this report is to describe the application of three of these methods to experimental and clinical data obtained from the Aberdeen Section Scanner (Bowley *et al.*, 1973).

The Reconstruction Problem

Figure 1 illustrates the problem and defines the term *projection* as used in this report. The function $g(x, y)$ is generally considered to be a density function. In radioisotope imaging it is the amount of radioactivity per unit area, assuming a uniform slice S of constant thickness. With a dual detector scanner a *projection* is ideally the counts recorded in a given time, at one position x', representing the integral of the activity over line L, the central axis of the detectors. (We ignore sensitivity variations and attenuation for the moment.) After the detectors have performed one scan, traversing the slice in the direction of x', we know $P_\theta(x')$ for all values of x', *i.e.* a *profile* at angle θ to some arbitrary base line. With the detectors rotated relative to the slice, at a different angle, another scan line produces another profile. The problem is to deduce or "reconstruct" $g(x, y)$ given a set of N such profiles, usually equally spaced throughout 180 deg. The scanner could of course be replaced by a gamma-camera; a single exposure produces the required profile and several slices, parallel to S, can then be examined simultaneously.

It is convenient to take the x axis as base line. Each profile can then be specified as a function of x' only where x', y' are the customary Cartesian axes in the rotated system. An arbitrary point (x, y) is seen during a scan at an arbitrary angle θ. Then from Fig. 1

$$x' = OQ = x \cos\theta + y \sin\theta \quad . \; . \; . \; . \; . \quad (1)$$

Note that the integral of any one profile yields the total radioactivity T within the slice:

$$T = \iint g(x, y)\, dx\, dy = \int P_\theta(x')\, dx' \quad . \; . \quad (2)$$

Reconstruction Methods

A brief summary of some of the available reconstruction methods will be given and the realization of three of these methods using a Digital Equipment Corporation PDP8 I computer. (For a more thorough review of algorithms see, for example, Smith, Peters and Bates, 1973; Gordon and Herman, 1974.) Programs were written in DEC 4K FORTRAN and PAL III. In practice, 30 equally-spaced profiles with 64 values in each, are manipulated to reconstruct an image within a 64×64 element array.

1. *Back projection* ("*Method 1*") (B.P.)

An approximate solution is given by back projection, where the reconstructed density at a point is assumed to be given by the addition of all projections through that point.

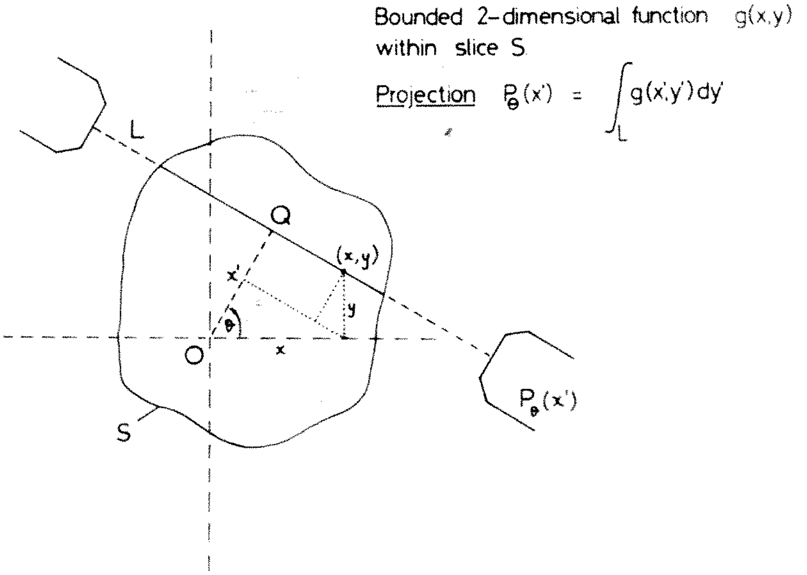

Bounded 2-dimensional function g(x,y)
within slice S
Projection $P_\theta(x') = \int_L g(x',y')dy'$
L
Q
(x,y)
x'
θ
y
O
x
S
$P_\theta(x')$

FIG. 1.

The reconstruction problem. After one scan pass, we know $P_\theta\ (x')$ for all values of x', *i.e.* a *profile* at angle θ. The problem is to deduce $g(x, y)$ given a set of N such profiles.

A high background is inevitably obtained and a background constant may be subtracted (Vainstein, 1970; Gilbert, 1972):

$$\underset{\text{B.P.}}{g(x, y)} = \sum_{\theta} P_\theta(x') - (N-1)T \qquad . \quad . \quad . \quad (3)$$

Each value of θ specifies one profile; the value of x' specifies that projection through the point to be reconstructed, and is given by equation (1). N is the total number of profiles and T is defined by equation (2).

As long as $g(x, y)$ has a highly peaked structure, these peaks will appear in the reconstruction, so the method may be said to give an approximate solution. The centre of the 64×64 array is taken as origin of the Cartesian co-ordinates x, y. Each element within the array receives 30 values, one value from each profile. The particular value to take from each profile is calculated using equation (1). Four minutes computation time is required. The background term in equation (3) is taken into account on display, *i.e.* only elements containing more than $(N-1)T$ are displayed.

2. *Fourier analysis*

Before proceeding to several more exact reconstruction schemes, it is worth considering the implications of some operations in Fourier space (X, Y). Knowing $g(x, y)$ we could perform the two-dimensional Fourier transform to produce $G\ (X, Y)$, or, inversely, knowing $G\ (X, Y)$ we could perform the inverse Fourier transform to obtain $g\,(x, y)$. A relevant Fourier theorem states that the Fourier transform of a profile is identical to a corresponding section through $G\,(X, Y)$. Hence we could build up $G\,(X, Y)$ on a square lattice of points, say, from the Fourier transforms of the known profiles using interpolation to deduce values at the actual grid points. An inverse transform then yields the required $g\,(x, y)$ (Crowther, De Rosier and Klug, 1970; Kay, Keyes and Simon, 1974).

This analysis provides insight into the *number of profiles required*. If the maximum dimension across $g\,(x, y)$ is D then in general it can only be determined in full if its Fourier transform is known on a square lattice of points spaced less than or equal to $1/D$ (Bracewell, 1958). If we have N equally-spaced profiles, *i.e.* an angular interval of π/N, than at a radial distance R_m (from the origin of X, Y co-ordinate system) the distance between *known* data will be $\pi R_m/N$.

Thus, providing

$$\frac{\pi R_m}{N} \leqslant \frac{1}{D} \qquad . \quad . \quad . \quad (4)$$

then $g(x, y)$ could be determined out to a limiting spatial frequency R_m. If $g\,(x, y)$ is a smooth function containing no spatial frequencies in excess of R_m then an accurate reconstruction is achieved. (Strictly, there is no exact solution obtainable with a finite number of profiles. If $g(x, y)$ is a space-limited function with maximum dimension D then an infinite spectrum of spatial frequencies is necessary for complete specification and if $R_m \rightarrow \infty$ then N must also. In practice, because of noise, there will be an upper limit to spatial frequency, beyond which the noise power exceeds signal power, say. Hence R_m and N may be restricted and condition 4 satisfied. Bracewell and Riddle (1967) discuss the errors in relaxing condition 4 for one specific application—reconstructing a frequency-limited point spread function.)

However, redundancy is apparent in the Fourier reconstruction steps and there exist more direct ways of obtaining an accurate estimate of $g(x, y)$. One such scheme consists essentially of modifying the original profiles such that when they are "back projected", an accurate estimate results. The modification required is to amplify spatial frequencies, the amplification being proportional to the frequency. In practice it may be implemented in two ways.

3. *Method 2* (*Bracewell and Riddle*) (B.R.)

The amplification of spatial frequencies is most obvious from the method of Bracewell and Riddle (1967). Modified profiles $H_\theta(x')$ are formed from the original profiles thus:

$$H_\theta(x') = P_\theta(x') * R_m\left[\frac{\sin 2B}{B} - \left(\frac{\sin B}{B}\right)^2\right] \quad . \quad . \quad (5)$$

where $B = \pi R_m x'$
and the symbol * represents the convolution operation. The *effect* of the operation is to multiply the Fourier transform of the profiles with a ramp function (*i.e.* amplification directly proportional to spatial frequency) out to a limiting spatial frequency R_m. Any spatial frequencies above R_m will be removed. The reconstructed density at a point is then given by the integral of all the *modified* projections through that point:

$$\underset{\text{B.R.}}{g(x, y)} = \int_0^\pi H_\theta(x')\, d\theta$$

which, for the discrete case of a finite number of profiles becomes

$$\underset{\text{B.R.}}{g(x, y)} = \frac{\pi R_m}{N} \sum_\theta H_\theta(x') \quad . \quad . \quad . \quad (6)$$

where again the value of x' for each profile is given by equation (1) and $\pi R_m/N$ is a normalization factor. If $g(x, y)$ is a smooth function containing no spatial frequencies in excess of R_m and limited in extent within the restriction imposed by condition 4 then an accurate estimate is achieved using equation (6).

In the realization of this method, a symmetric non-recursive digital filter with 31 weighting values W_i was used as the convolution function, *i.e.*

$$W_i = W_{-i} = \left[\frac{\sin 2\pi R_m i\Delta}{\pi R_m i\Delta} - \left(\frac{\sin \pi R_m i\Delta}{\pi R_m i\Delta}\right)^2\right]\left(0{\cdot}54 + 0{\cdot}46 \cos \frac{2\pi i}{31}\right)$$

for $i = 0, 1 \ldots 15$. Δ is the interval at which the data from the scanner were sampled, typically 4 mm. The cosine term is a "window function", a recognized smoothing procedure (Gold and Rader, 1969) necessary to prevent oscillations due to *truncation* of the convolution function after 15 values, and useful to reduce statistical noise in the data. The weighting values and frequency responses of three such filters are shown in Table I and Fig. 2. The number of weighting values, 15 on either side of the central value $W_0 = 1$, was arbitrarily chosen as a suitable compromise between accuracy and computational speed. On the PDP8I, convolution of a single profile takes approximately four seconds. Total assembly time for 30 profiles is therefore approximately six minutes.

TABLE I

Weighting values W_i of the 31-point symmetric non-recursive digital filter used as the convolution function in Method 2, listed to four decimal places, for $R_m = 0{\cdot}4$ cm^{-1} and $\Delta = 0{\cdot}4$ cm; $W_i = W_{-i}$ and $W_0 = 1$.

i	W_i
1	+0·7540
2	+0·1874
3	−0·3257
4	−0·5019
5	−0·3393
6	−0·0589
7	+0·1119
8	+0·1072
9	+0·0145
10	−0·0515
11	−0·0506
12	−0·0156
13	+0·0100
14	+0·0134
15	+0·0051

4. *Method 3* (*Radon*) (R)

A method of modifying the profiles by differentiation followed by convolution with $1/x'$ has been proposed by Berry and Gibbs (1970) and Gilbert (1972). The method appears to be identical to that of Radon (1917), recently described by Cormack (1973). Gilbert (1972) describes the effect of the method on the spatial frequencies in the profiles—amplification directly proportional to spatial frequency, with no upper limit. Radon's method has been formulated in several different ways, but following the above notation we first perform

$$\bar{P}(r) = \frac{1}{2\pi}\int_0^{2\pi} P_\theta(x' - r)\, d\theta \quad . \quad . \quad . \quad (7)$$

i.e. average all the projections at distance r from the point to be reconstructed.

Then

$$\underset{\text{R}}{g(x, y)} = \frac{-1}{\pi}\int_0^\infty \frac{d\bar{P}}{r} \quad . \quad . \quad . \quad (8)$$

The similarity with differentiation and convolution with $1/x'$ is apparent.

Radon's reconstruction is general. The method of Bracewell and Riddle will perform the same task for data with a limited spatial frequency content, a necessary condition if a finite number of profiles are to suffice, according to condition 4. Since the steps in Radon's reconstruction are equivalent to differentiation *and* convolution with $1/x'$, the single convolution operation of Bracewell and

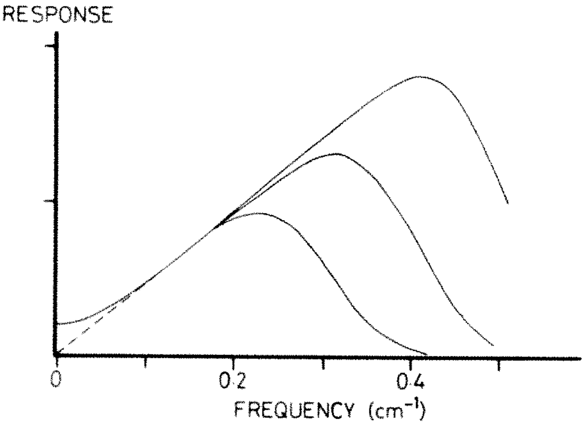


Fig. 2.

Frequency-response curves of the 31-point symmetric non-recursive digital filters used as the convolution function in Method 2; an example of the actual weighting values is listed in Table I. The filters were designed with "cut-off frequency" R_m equal to 0·5, 0·4 and 0·3 cm^{-1} respectively. The desired response (dotted line) can be more closely approximated by using a larger number of points.

Riddle would seem the method of choice. However, both methods have been included for comparison. Smoothing to reduce statistical noise, a desirable process with noisy radioisotope data, can be readily incorporated. Indeed Tanaka *et al.* (1973) describe a convolution function incorporating Gaussian smoothing to be used in place of equation (5).

In the realization of Radon's method, equation (7) is replaced by the discrete sum

$$\overline{P}(r)=\frac{1}{N}\sum_{\theta}\Big(P_\theta(x'-r)+P_\theta(x'+r)\Big)$$

and equation (8) is replaced by

$$\underset{\mathrm{R}}{g}(x,y)=\frac{1}{\pi}\sum_{i}\frac{\overline{P}(r_i)-\overline{P}(r_{i+1})}{\frac{1}{2}(r_i+r_{i+1})} \quad . \quad . \quad . \quad (9)$$

and since for discrete data, $r_i=i\Delta$, equation (9) becomes

$$\underset{\mathrm{R}}{g}(x,y)=\frac{2}{\pi\Delta}\left[\overline{P}(O)-2\sum_{i=1}^{63}\frac{\overline{P}(i)}{4i^2-1}\right]$$

It is interesting to note that: (1) $\overline{P}(O)$ is the "back-projected" value as in Method 1, before background subtraction, and (2) whereas "back projection" used only one value from each profile to estimate $g(x, y)$ at one point, Radon's reconstruction requires knowledge of $P_\theta(x')$ throughout the entire plane as in fact does the convolution method of Bracewell and Riddle. Fifteen minutes computation time is required, approximately two and a half times that of Method 2. The speed in Method 2 is gained by truncating the convolution function after 15 values, introducing the approximation illustrated in Fig. 2—accuracy may be sacrificed for speed.

APPLICATION

The three assembly methods have been used to reconstruct a section scan taken around a "brain phantom". The reconstructed images are presented as they appear on the display oscilloscope (intensity modulated grey scale), Fig. 3.

Method 1 produces an image which is "built up" in the centre. Gilbert (1972) shows that this image in fact represents a convolution of the true image with a known function (which tends to the form $1/r$ in the limiting case of an infinite number of profiles).

Methods 2 and 3 produce more accurate images; with this simple phantom the "true image" is obtained by a conventional area scan over the upright bottles, illustrating that the bottles were in fact uniformly filled. Since no smoothing is implicit in the realization of Radon's method the original profiles are twice smoothed with a linear three-point average process to reduce statistical fluctuations prior to reconstruction using Method 3. The effects of sensitivity variation and attenuation are better appreciated on reconstructions using Methods 2 and 3; the bottle images appear elongated (in the direction of least attenuation) and in fact the bottles near the centre appear of slightly lower intensity than those near the periphery. (With Method 1 the assembly process itself masks this latter effect.) However, for a section of comparable dimensions, reconstructions using Methods 2 or 3 would appear to be reasonably quantitative.

Figure 4 illustrates the assembly methods applied to an actual brain scan. Method 2 smooths high spatial frequency components of the image slightly more than Method 3, but no real detail would appear to be lost. As with "processed" conventional γ-ray images, no firm conclusions can be stated as to which method produces the "better" image, the choice being largely subjective. Experience to date suggests that the methods be used according to the statistical accuracy of the data. With very low-count density images Method 1 is probably all that can be usefully applied. With currently available count densities the use of Methods 2 and 3, as described above, appears justified. If more accurate data were obtainable, more emphasis could be placed on higher spatial frequencies and Methods 2 and 3 adapted accordingly.

ABSORPTION AND SOLID ANGLE FACTORS

With γ-ray imaging devices, the raw data do not quite conform to the requirement of true line integrals, as observed by Cormack (1973).

Firstly, there is the "finite field of view" of the γ-ray detection equipment which has an effect both within the plane of the section and perpendicular to it. Within the plane, it implies that the best reconstruction obtainable would be equivalent to a conventional scan of the isolated section. Perpendicular to the plane of the section, the z-axis of Cartesian co-ordinates, it implies that only if $g(x, y, z)$ is independent of z, at least throughout the field of view, will an accurate reconstruction of $g(x, y)$ be meaningful and *quantitative, i.e.* representative of the true concentration of radioactivity over the specified plane. If the field of view varies appreciably throughout the section, quantitative results are virtually impossible. This field of view or sensitivity variation has been termed the solid angle factor by Cormack (1973). It can be studied by moving a point or line source in air over the region between the two detectors.

Secondly, there is absorption within the medium containing the radioactivity, the absorption factor.

Thus the profiles detected will generally be of the form.

$$D_\theta(x, y)=\int_L f(x, y)\, g(x, y)\, dy' \quad . \quad . \quad . \quad (10)$$

where $f(x, y)$, containing both the solid angle and absorption factors, varies throughout the plane.

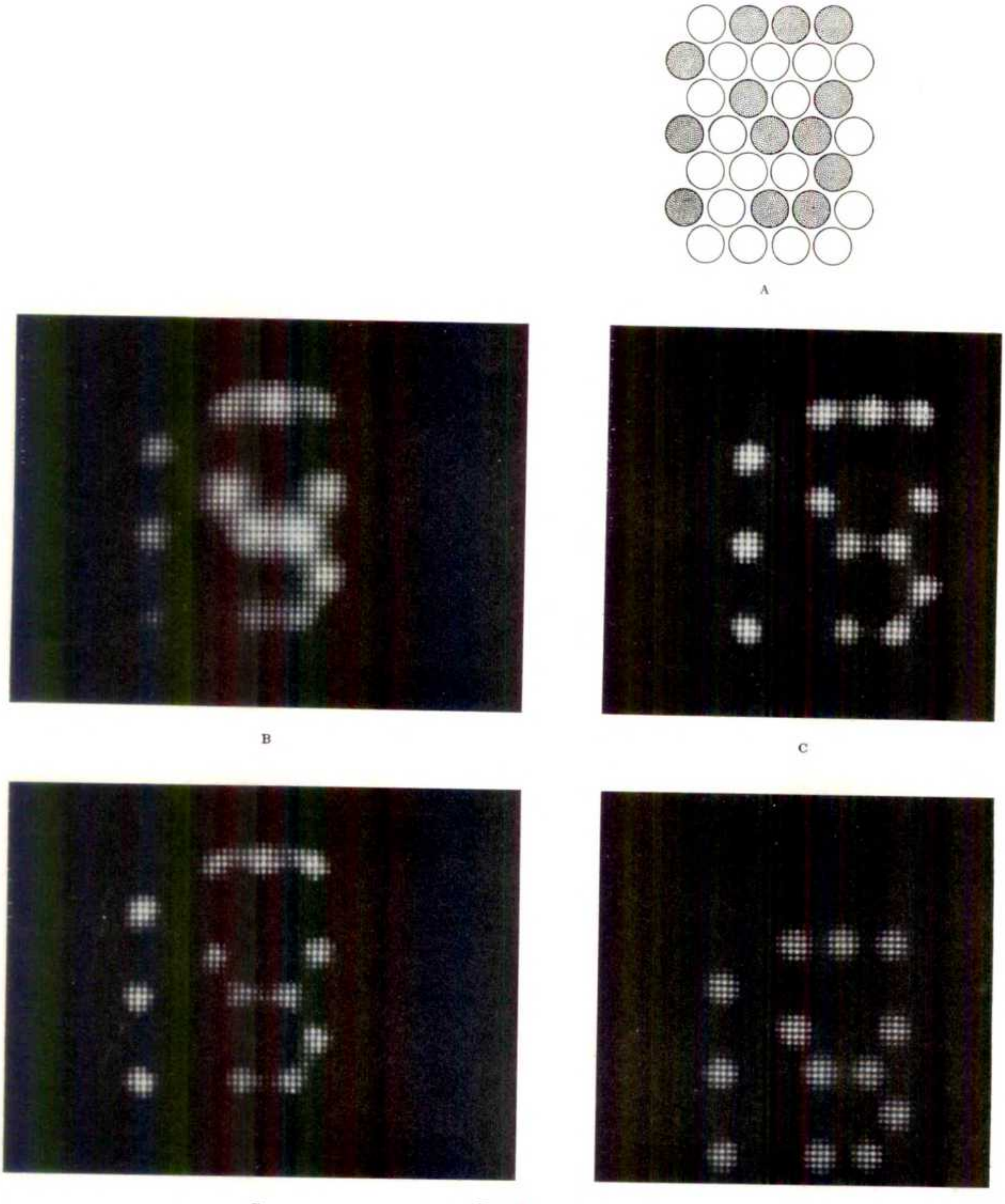


FIG. 3.

A section scan was performed around a phantom made up of a collection of bottles containing either water or equal amounts of ^{99}Tc^{m}, shown hatched (A). The overall size was 19 × 15 cm. Reconstructions using Methods 1, 2 and 3 are shown in (B), (C) and (D) respectively. In Method 2, R_{m} was 0·4 cm^{-1}. The "true image", a conventional area scan over the upright bottles is shown in (E). Methods 2 and 3 are seen to produce results which are similar, and quantitatively more accurate than Method 1. Element size is 4 mm.

If the two factors can be combined such that $f(x, y)$ becomes simply a function of *total thickness* of absorbing medium, then

$$f(x, y) \equiv f(x')$$

and equation (10) becomes

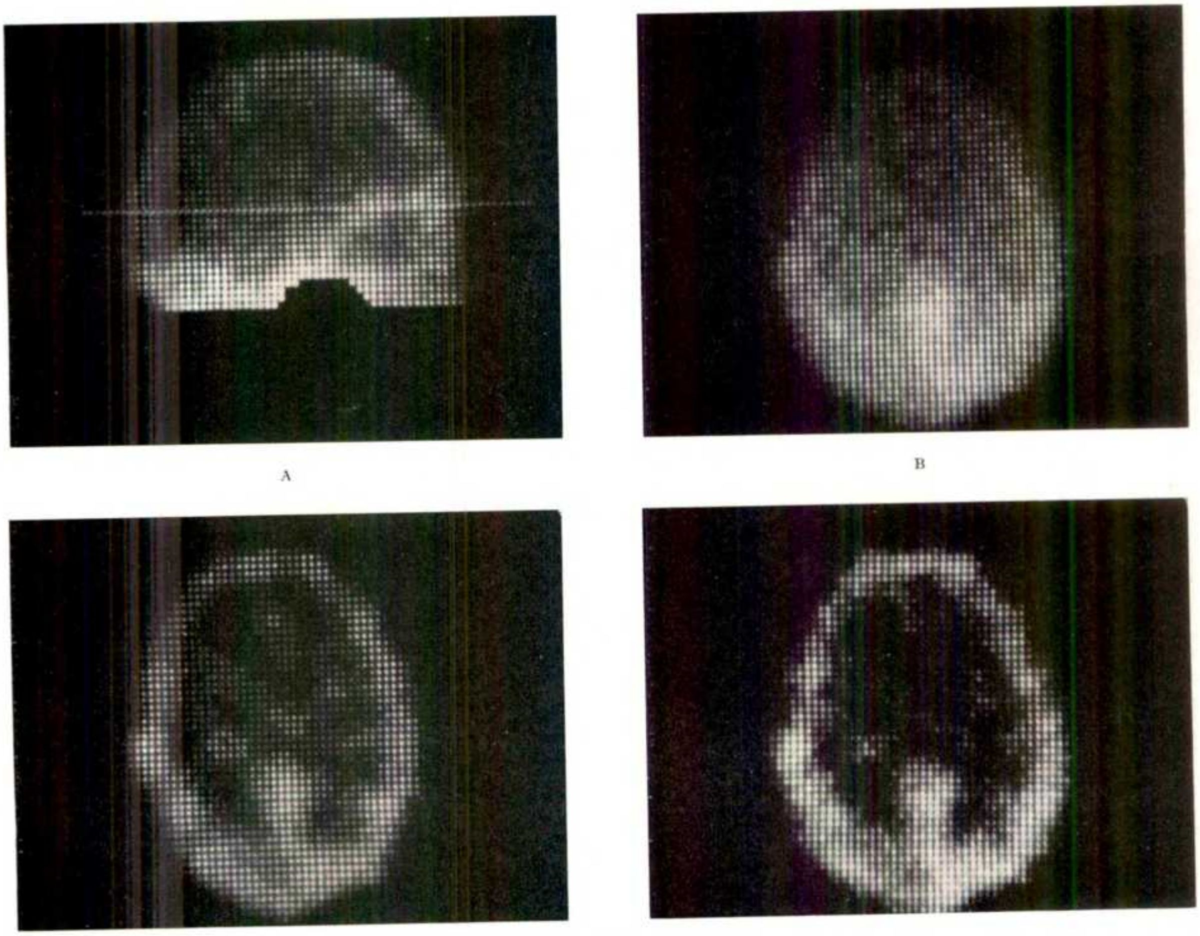
$$D_\theta(x') = f(x') \int_L g(x, y)\, dy'$$

Hence the true line integral can be obtained by correcting the observed profiles, *i.e.*

$$P_\theta(x') = \frac{D_\theta(x')}{f(x')}$$

Experiments have indicated that with the Aberdeen Section Scanner, *i.e.* 3½ in. diameter crystal detectors, long-focusing collimators (Myers and Mallard, 1964) and substantial inter-collimator distance (40 cm), $f(x, y)$ can within reasonable limits be considered an exponential function of total thickness L of absorbing medium (Fig. 5). The best form of $f(x')$ was found experimentally to be

$$f(x') = \frac{1}{\mu L}\left(1 - e^{-\mu L}\right)$$



A

B

C

D

FIG. 4.

^{99}Tc^{m} brain scan showing a lesion in the posterior fossa: (A) conventional lateral view illustrating the position of the section scan; reconstructions of the section scan using Methods 1, 2 and 3 are shown in (B), (C) and (D) respectively. Method 2 ($R_m = 0{\cdot}4$ cm^{-1}) smooths high spatial frequency components of the image slightly more than Method 3, but no real detail is lost. Element size is 4 mm.

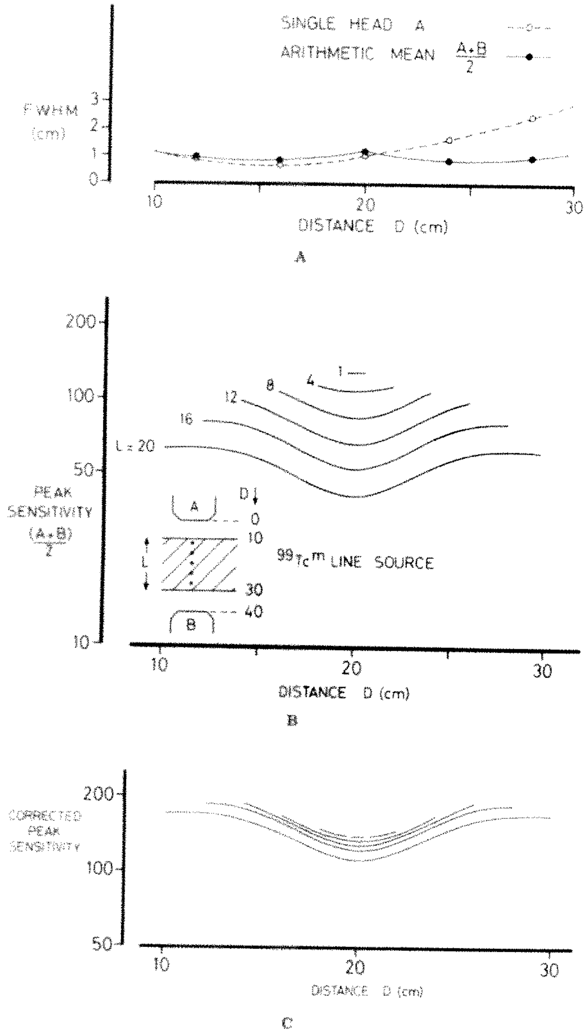


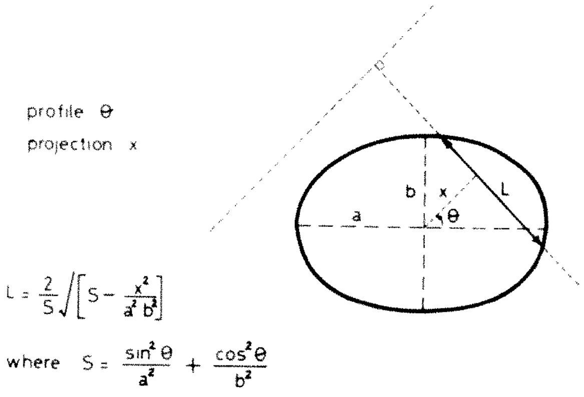
Fig. 5.

Sensitivity and field of view variations for the ASS $^{99}Tc^m$ 15 cm focus collimators; inter/collimator separation 40 cm; energy window 110–180 keV.

(A) The "field of view", as defined by the full-width at half-maximum of the line spread function, is reasonably constant.

(B) The peak sensitivity (counting rate at the maximum of the line spread function) is also relatively independent of distance ±20 per cent and approximately an exponential function of slab thickness L, with effective HVL 5·6 cm of tissue equivalent MIX D.

(C) The effect of attenuation correction on the peak sensitivity curves.



$$L = \frac{2}{S}\sqrt{\left[S - \frac{x^2}{a^2 b^2}\right]}$$

$$\text{where } S = \frac{\sin^2\theta}{a^2} + \frac{\cos^2\theta}{b^2}$$

Fig. 6.

Calculation of the chord length for an ellipse. Two measurements, the major and minor axes, are sufficient to specify the thickness L for any projection at distance x from the centre of the ellipse.

where μ is an effective attenuation coefficient. The effect of dividing the peak sensitivity by this factor is shown in Fig. 5c, the object being to produce the same corrected number of counts from the line source irrespective of position between the detectors or thickness L of tissue. This was achieved to within ±27 per cent. The ***additional*** information required to obtain $f(x')$ is the thickness of the object for each projection, a considerable amount of data. A practical compromise would be to represent the patient and supporting couch by an ***ellipse*** of homogenous material. Two thicknesses, the major and minor axes are then sufficient to specify the thickness for each projection (Fig. 6).

This form of attenuation correction which takes an extra three minutes computation time was tested on a section scan of a uniformly-filled torso phantom with elliptical cross-section (data manipulated using Method 2), Fig. 7. The phantom dimensions are now considerably greater than in Fig. 3 and absorption effects will be greater. Without correction more activity is attributed to the superficial rim compared to the actual distribution; this effect is masked around the lower rim due to the couch supporting the phantom. After correcting the profiles, the reconstructed image is quantitatively a more accurate representation of the actual distribution. The counting density was similar to that obtained from an actual liver section scan; the noise due to counting statistics is apparent. Display is on a confidence interval basis, each discrete grey level representing an interval of three "standard deviations" of the count density range (Keyes, Barber and Mallard, 1973). The derivation of "standard deviation" in the reconstructed data is tentative and is still under investigation.

Finally, Fig. 8 illustrates the same processing applied to an actual liver scan.

SUMMARY

Transverse section γ-ray imaging is a relatively new procedure which appears already to be clinically valuable. Caution is needed in selecting and testing (a) collimation systems, to ensure the collection of meaningful data, and (b) reconstruction methods, to make the best use of these data. In the present work the use of long-focus collimators was examined. The reconstruction method of Bracewell and Riddle (1967) was found convenient since then the data were manipulated in a manner where *smoothing* to reduce statistical noise and *correction* for attenuation could both be readily incorporated. Computation could be performed reasonably quickly on modest equipment. It is to be expected that many different algorithms will produce similar results since this is a general feature of digital filtering (Gold and Rader, 1969).

The reconstructed image is a density distribution, ideally concentration of radioisotope per unit area in the plane of the section. However, in practice a quantitative estimate is only achieved if (a) the concentration does not vary significantly over the thickness of the section, and (b) the thickness of the section viewed by the collimation system is reasonably constant over the plane of the section. These are restrictive conditions viewed pessimistically by Cormack (1973) and optimistically by Budinger and Gullberg (1974), but the technique, even if never strictly quantitative, has a lot to offer in assisting the visualization and approximate quantitation of a three dimensional distribution of radioactivity *in vivo*.

ACKNOWLEDGMENTS

I am indebted to my colleagues Drs. D. C. Barber, J. N. S. Hutchison, M. J. Myers and P. E. Undrill for much helpful discussion and assistance with this work; also to Dr. A. F. MacDonald, consultant radiologist, Aberdeen Royal Infirmary, and to Professor J. R. Mallard, Head of the Medical Physics Department, Aberdeen University, whose insight, enthusiasm and determination gave rise to the Aberdeen Section Scanner project.

REFERENCES

BERRY, M. V., and GIBBS, D. F., 1970. The interpretation of optical projections. *Proceedings of the Royal Society, A*, *314*, 143–152.

BOWLEY, A. R., TAYLOR, C. G., CAUSER, D. A., BARBER, D. C., KEYES, W. I., UNDRILL, P. E., CORFIELD, J. R., and

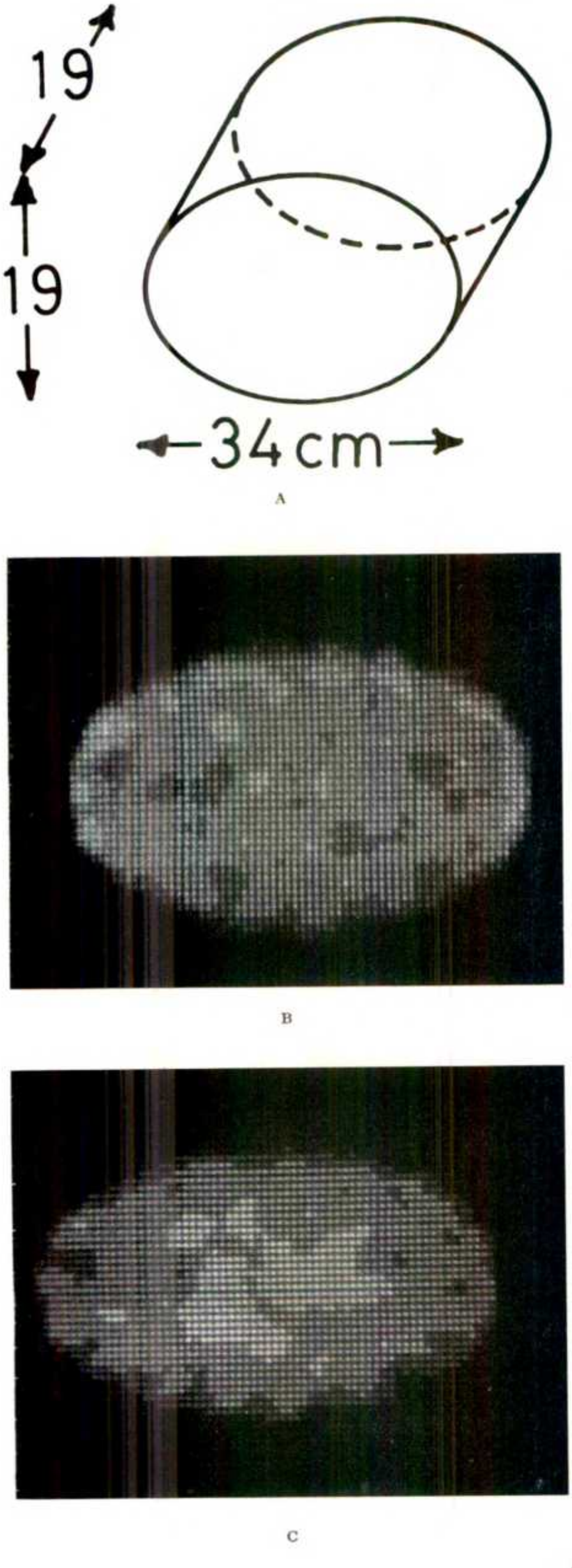
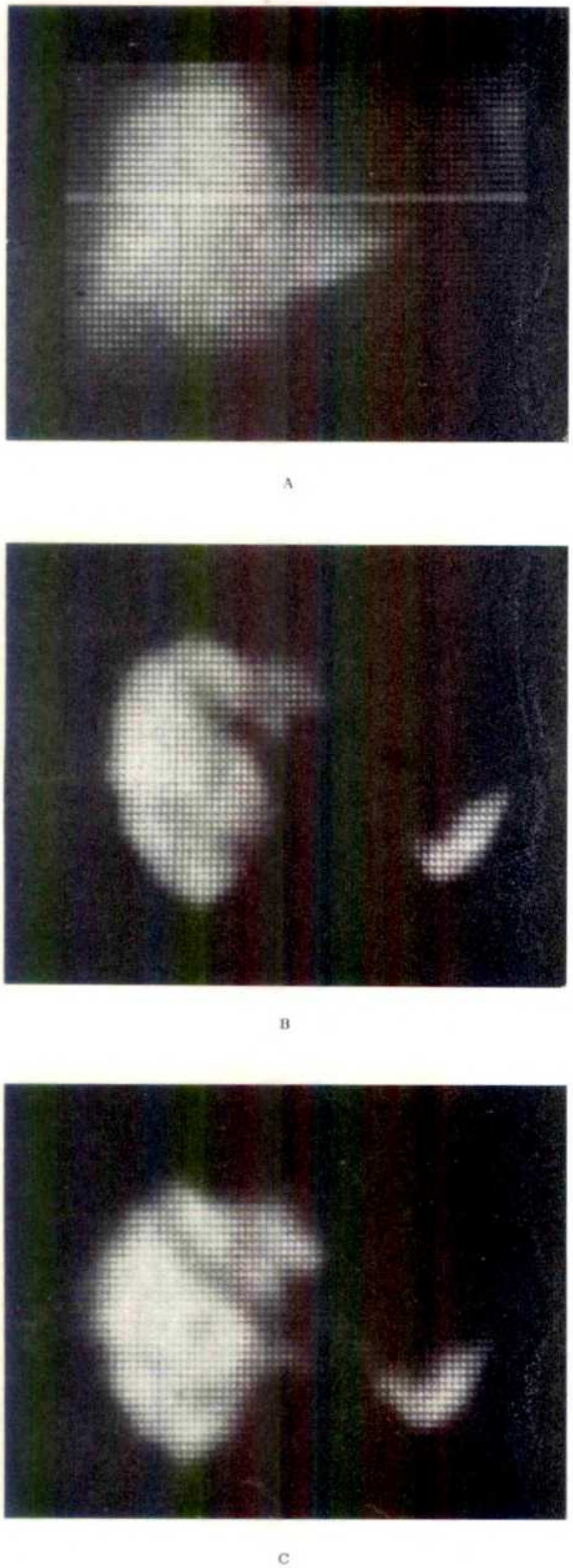


FIG. 7.

Section scan of a torso phantom with elliptic cross-section uniformly filled with ^{99}Tc^{m}: (A) phantom dimensions; reconstructions using Method 2 ($R_m = 0{\cdot}32$ cm^{-1}) are shown, (B) before and (C) after correcting the original scan profiles for attenuation. With uncorrected profiles more counts are attributed to the superficial rim compared to the true distribution. Element size is 5 mm.


A

B

C

FIG. 8.

^{99}Tc^{m} sulphur colloid scans of liver on a patient with persistently raised liver function tests: (A) conventional anterior view illustrating the position of the section scan, (B) reconstruction of the section using Method 2 ($R_m = 0{\cdot}32$ cm^{-1}) without attenuation correction, (C) with attenuation correction. Element size is 5 mm.

MALLARD, J. R., 1973. A radioisotope scanner for rectilinear, arc, transverse section and longitudinal section scanning. *British Journal of Radiology*, *46*, 262–271.

BRACEWELL, R. N., 1958. Radio interferometry of discrete sources. *Proceedings of the Institute of Radio Engineers*, *46*, 97–105.

BRACEWELL, R. N., and RIDDLE, A. C., 1967. Inversion of fan-beam scans in radio-astronomy. *Astrophysical Journal*, *150*, 427–434.

BUDINGER, T. F., and GULLBERG, G. T., 1974. Three-dimensional reconstruction of isotope distributions. *Physics in Medicine and Biology*, *19*, 387–389.

CORMACK, A. M., 1973. Reconstruction of densities from their projections, with applications in radiological physics. *Physics in Medicine and Biology*, *18*, 195–207.

CROWTHER, R. A., DE ROSIER, D. J., and KLUG, A., 1970. The reconstruction of a three-dimensional structure from projections and its application to electron microscopy. *Proceedings of the Royal Society*, *A*, *317*, 319–340.

GILBERT, P. F. C., 1972. The reconstruction of a three-dimensional structure from projections and its application to electron microscopy, II. Direct methods. *Proceedings of the Royal Society B*, *182*, 89–102.

GOLD, B., and RADER, C. M., 1969. In *Digital Processing of Signals*, pp. 226–232 (McGraw-Hill Book Company Inc., New York).

GORDON, R., and HERMAN, G. T.,1974. Three-dimensional reconstruction from projections: A review of algorithms. *International Review of Cytology*, *38*, 111–151.

HOUNSFIELD, G. N., 1973. Computerized transverse axial scanning (tomography): Part I. Description of system. *British Journal of Radiology*, *46*, 1016–1022.

KAY, D. B., KEYES, J. W., and SIMON, W., 1974. Radionuclide tomographic image reconstruction using Fourier transform techniques. *Journal of Nuclear Medicine*, *15*, 981–986.

KEYES, W. I., BARBER, D. C., and MALLARD, J. R., 1973. Quantitative multi-level display of scan data via a small digital computer. *Physics in Medicine and Biology*, *18*, 133–137.

KUHL, D. E., and EDWARDS, R. Q., 1964. Cylindrical and section radioisotope scanning of the liver and brain. *Radiology*, *83*, 926–936.

MYERS, M. J., and MALLARD, J. R., 1964. Long focusing depth independent collimators for *in-vivo* radioisotope scanning. *International Journal of Applied Radiation and Isotopes*, *15*, 725–739.

RADON, J., 1917. Über die Bestimmung von Funktionen durch ihre integralwerte längs gewisser Mannigfaltigkeiten. (On the determination of functions from their integrals along certain manifolds.) *Berichte Sächsische Akadamie der Wissenschaften* (*Leipzig*) *Mathematische-Physische Klasse*, *67*, 262–277.

SMITH, P. R., PETERS, T. M., and BATES, R. H. T., 1973. Image reconstruction from finite numbers of projections. *Journal of Physics*, *A*, *6*, 361–382.

TANAKA, E., SHIMIZU, T., IINUMA, T., and FUKUHISA, K., 1973. Digital simulation of section image reconstruction. In *National Institute of Radiological Sciences*, *Annual Report 1972* (Science and Technology Agency, Japan).

VAINSTEIN, B. K., 1970. Finding the structure of objects from projections. *Kristallografiya*, *15*, 894–902. Translated in *Soviet-Physics – Crystallography*, *1971*, *15*, 781–787.

1976, *British Journal of Radiology*, *49*, 71–75 JANUARY 1976

A modified geometric factor approach to internal gamma ray dosimetry

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Received March, 1974 and in revised form April, 1975)

ABSTRACT

In internal γ-ray dosimetry, the conventional geometric factor approach, where the "effective absorption coefficient" is taken as 0 or 0·028 cm^{-1}, irrespective of source energy, leads to significant errors especially in the low energy region. An ettempt has been made in this paper to modify the approach to increase the accuracy of calculation and to extend its usefulness to low energies while retaining its inherent simplicity. The modification consists in replacing the effective absorption coefficient by the attenuation coefficients appropriate to the source energies and taking into account the effects due to multiple scattering by using point source build-up factor. The method has been applied for the particular case of dosimetry of a sphere. Comparison of the results obtained by this method with those got from Monte Carlo computations indicates excellent agreement at higher energies and a departure of around 15 per cent only at lower energies (as against a variation of 400 per cent when conventional geometric factor approach is used).

In the dosimetry of internal gamma emitters, the geometric factor concept developed by Marinelli, Quimby and Hine (1948) has proved to be a simple and elegant approach. In this method the effective absorption coefficient is taken as either 0 or 0·028 cm^{-1} (0 for linear dimensions less than 10 cm and 0·028 cm^{-1} for larger dimensions), irrespective of source energy. This technique was found to be satisfactory for clinical radium dosimetry as absorption coefficients do not vary significantly in the energy range between 0·1 MeV and 1·0 MeV. Geometric factors for simple shapes, *e.g.* sphere (Marinelli *et al.*, 1948; Bush, 1949; Trucco, 1964) and cylinder (Mayneord, 1950; Kovalev, 1958) were calculated. Tables for average geometric factors were published by Loevinger, Holt and Hine (1956) and by Focht, Quimby and Gershowitz (1965).

Two parallel developments occurred which altered this simple approach, namely:

(1) development of Monte Carlo methods for γ-ray dose calculations; and

(2) increased use of low energy gamma-emitters for clinical purposes (*e.g.* ^{125}I, ^{99}Tc^{m}) in nuclear medicine.

The Monte Carlo approach is general, can take into account boundary conditions, and give accurate dose computations, specially with the availability of powerful computers over the last few years. It became evident that doses calculated by the simple geometric factor approach gave results that were in great error particularly at low energies, (~400 per cent at 20 keV) (Ellett, 1969). The application of Monte Carlo computation technique to new situations involves a substantial demand on computer time.

An attempt has been made here to examine the possibility of modifying the conventional geometric factor approach in order to improve the accuracy of calculation and to extend its usefulness to low photon energies while retaining its inherent simplicity. The modification consists in replacing the effective absorption coefficient by the attenuation coefficients appropriate to the source energies and taking into account the effects due to multiple scattering by using point source dose build-up factors. This approach is basically similar to the ideas developed by Loevinger *et al.* (1956) and formally restated by Loevinger and Berman (1968). Berger (1968) using infinite dose build-up factors gave a range of absorbed fractions for spheres surrounding a point source of radioactivity. In the present paper, the modified geometric factor method has been applied for the specific case of a spherical source to compute the geometric factor at any point, as well as the average geometric factor. For ease of comparison, absorbed fractions are calculated from the average geometric factor following the approach given by Quimby, Fietelberg and Gross, (1970). The absorbed fractions so calculated have been compared with those available from the Monte Carlo computations (Reddy, Ellett and Brownell, 1967; Brownell, Ellett and Reddy 1968) and it is shown that the two methods give results of comparable accuracy.

DOSE CALCULATION BY MODIFIED GEOMETRIC FACTOR APPROACH

The absorbed dose rate *R*p at any point *P* inside a uniform internal distribution of activity in a homogeneous absorbing medium is given by

$$Rp = 10^{-3} \,.\, \Gamma a \,\frac{A}{m}\,.\, g_p \text{ rad/h} \quad . \quad . \quad . \quad (1)$$

where, g_p the modified geometric factor is given by

$$g_p = \int \frac{\exp(-\mu x)}{x^2} \cdot B(\mu x) dV$$

Γa = Photon absorbed dose constant

$= 169{\cdot}8\,(\mu_a/\rho)\,E_\gamma \dfrac{\text{Cm}^2\ \text{rad}}{\text{mCi . h}}$ (Greenfield and Lane, 1971)

μ_a/ρ = Photon mass absorption coefficient for primary photon energy (cm^2/g)

A = Activity (μCi)

m = Mass of the medium (g)

$B(\mu x)$ = Point source energy build-up factor (Berger, 1968)

μ = Photon attenuation coefficient at source energy (cm^{-1})

x = Distance of volume element, dV, from the point P (cm)

Similarly the average absorbed dose rate $\bar{R}$ to a volume V containing the activity is given by

$$\bar{R} = 10^{-3}\,\Gamma a \frac{A}{m} \bar{g} \text{ rad/h} \quad . \quad . \quad . \quad (2)$$

where

$$\bar{g} = \frac{1}{v} \int g_p \, dV$$

In the special case of a sphere (Fig. 1), the expression for g_p becomes (Reddy, Gupta and Nagaratnam, 1961)

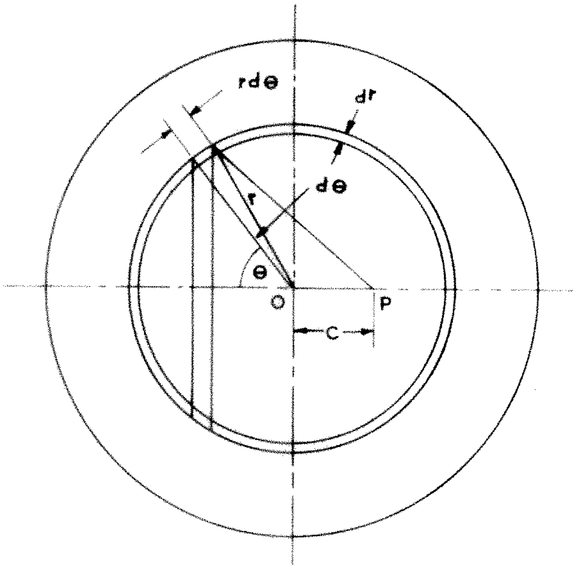

FIG. 1.

$$g = 2\pi \int_0^R \int_0^\pi \frac{r^2 \operatorname{Sin}\theta \, d\theta \, dr}{r^2 + c^2 - 2rc \cos\theta}$$

$$\exp\left(-\mu\sqrt{r^2 + c^2 - 2rc\cos\theta} \quad B\mu\sqrt{r^2 + c^2 - rc\cos\theta}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

It may be noted that Mayneord (1945) had worked out the dosimetry of a spherical source neglecting both attenuation and build-up. Later Trucco (1964), Fitzgerald, Brownell and Mahoney, (1968) and Hubbard and Williamson (1969) gave a detailed expression which took into account the effect due to self absorption.

The build-up factor is defined by different expressions, one of the most widely used being Taylor's Fit (1963). Using Taylor's Fit for the build-up factor, Sundaram, Gopinath and Ganguly (1965) gave an analytical expression for the dose rate at any point in a sphere for photon energies higher than 500 keV. However, the prime interest in nuclear medicine is in the use of lower photon energies and the expressions for the build-up factor are not readily available using Taylor's Fit. Berger fitted his tabulation of build-up factor in an infinite water medium (1968) by the polynominal expression, namely

$$B\ (\mu x) = 1 + \sum_{n=0} a_n\ (\mu x)^{n+1} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and gave the values of the polynomial coefficients, a_n. When equation (4) is substituted for build-up factor, equation (3) is not integrable analytically. In the present case, numerical integration has been made using values of a_n and μ as given by Berger (1968) for various energies and source sizes.

DOSE CALCULATION BY ABSORBED FRACTION

In the case of a uniform internal distribution of activity in a homogeneous absorbing medium, the average absorbed dose rate (Loevinger and Berman, 1968) is given by

$$\bar{R} = \frac{A}{m} \Sigma \phi_i \triangle_i \text{ rad/h} \quad . \quad . \quad (5)$$

where A = Activity (μCi)

m = Mass of the medium (g)

ϕ_i = Absorbed fraction for ith energy

$\triangle_i$ = Equilibrium dose constant $\dfrac{(\text{g.rad})}{\mu\text{Ci.h}}$ and is equal to $2{\cdot}13\ n_i\ \bar{E}_i$ (Loevinger and and Berman, 1968)

For monoenergetic photons the expression reduces to

$$\bar{R} = \frac{A}{m} \phi \triangle \text{ rad/h.} \quad . \quad . \quad . \quad (6)$$

TABLE I

Comparison of absorbed fraction from modified geometric factor (MGF) method and Monte Carlo method
(Spherical source: Uniform distribution of Activity)

Source Mass (g)	100		300		1000		5000	
Photon Energy keV	MGF	Monte Carlo	MGF	Monte Carlo	MGF	Monte Carlo	MGF	Monte Carlo
30	0·319	0·306	0·42	0·39	0·63	0·65	0·66	0·70
40	0·183	0·165	0·27	0·23	0·50	0·48	0·55	0·55
60	0·0949	0·087	0·15	0·14	0·34	0·30	0·40	0·36
80	0·0743	0·070	0·12	0·11	0·28	0·26	0·33	0·31
100	0·0683	0·067	0·105	0·107	0·25	0·24	0·30	0·29
200	0·0689	0·069	0·102	0·100	0·23	0·22	0·27	0·26
300	0·0707	0·070	0·103	0·102	0·22	0·21	0·26	0·25
400	0·0713	0·070	0·103	0·103	0·22	0·21	0·26	0·245
800	0·0678	0·067	0·0696	0·100	0·20	0·20	0·23	0·23
1,000	0·0655	0·066	0·0934	0·097	0·19	0·19	0·22	0·22

TABLE II

Comparison of absorbed fraction from Monte Carlo method and modified geometric factor (MGF) method applying dose reciprocity theorem
(Spherical Source: Activity at the Centre)

Photon Energy keV	30		40		60		100		600	
Source Mass (g)	Monte Carlo	MGF	Monte Carlo	MGF	Monte Carlo	MGF	Monte Carlo	MGF	Monte Carlo	MGF
10	0·185	0·218	0·088	0·106	0·043	0·0497	0·036	0·0374	0·041	0·0435
100	0·402	0·450	0·211	0·245	0·109	0·122	0·085	0·0886	0·091	0·0931
1,500	0·805	0·834	0·582	0·586	0·350	0·353	0·275	0·257	0·225	0·225
10,000	0·952	1·014	0·806	0·864	0·581	0·651	0·448	0·509	0·382	0·403
60,000	0·997	1·093	0·974	0·994	0·882	0·899	0·770	0·810	0·613	0·647

For source masses of 10,000 and 60,000 g, absorbed fraction values as obtained by Monte Carlo calculations have not been multiplied by back scattered radiation correction.

Equating expression (2) and (6) we get

$$\phi = 10^{-3} \frac{\Gamma a}{\triangle} \bar{g} \quad . \quad . \quad . \quad (7)$$

Results and Discussion

The values of absorbed fraction, ϕ, have been calculated using equation (7) and are listed in Tables I and II under the heading MGF. Γa values have been taken from Greenfield and Lane (1971) and are for unit density material (soft tissue). They are calculated using the values of μ_a/ρ appropriate to any given primary photon energy. The values listed under the heading "Monte Carlo" are also the values of absorbed fraction but are taken from Brownell *et al.*, (1968) and have been corrected for back scatter. These values are also for unit density material (tissue equivalent). The variation in Γ_a or ϕ values between different unit density materials like soft tissue and water is known to be within 5 per cent (Berger, 1968).

In the particular case when the activity is concentrated at the centre of the sphere, g_p can readily be obtained from the previous calculations (Gupta 1973) of g_p values at the centre of sphere with uniform distribution of activity by application of the Dose Reciprocity Theorem (Mayneord, 1945). Table II gives absorbed fractions obtained as above along with those obtained by Monte Carlo calculations for this case.

It can be seen from Tables I and II that the values of absorbed fraction as calculated by the two methods agree with each other within 17 per cent over the whole range of energy and phantom masses. The variation is more noticeable in the case of small source mass and low source energies. For source masses more than 1,500 g and at energies above 60 keV, the two methods give comparable results. Both the methods exhibit the same trend in the variation of absorbed fraction with energy, *i.e.* a decrease which is initially rapid and then slower. Above 100 keV there is only a marginal variation in AF with energy.

At lower energies, it has been reported that the conventional geometric factor technique gives values of absorbed dose very much higher; at 20 keV, higher than 400 per cent in comparison to those calculated by the Monte Carlo method (Ellett, 1969). The reason for this disparity is that, conventionally, in calculating absorbed dose by g, the true absorption coefficient has been taken as effective absorption coefficient which is given the value either 0 or $0{\cdot}028$ cm^{-1}. This situation would be approximately true for higher energies where absorption is partially compensated by scattered photons. In the lower energy region, the compensation due to scattered radiation is insignificant and therefore true absorption coefficient changes rapidly with energy. Thus dose calculation based on effective absorption coefficient is likely to be significantly in error. In the present calculation of geometric factor, the exact values of attenuation coefficients have been used and appropriate corrections have been applied for build-up, and so the argument is good at all energies. It may be pointed out that there may be a margin of around 5 per cent in the accuracy of numerical integration due to rounding off procedures (Ellett and Hume, 1971). This limitation applies both to Monte Carlo and to our present computation.

Conclusion

A modified geometric factor technique has been presented for calculating photon absorbed dose due to uniform distribution of activity in a homogeneous unit density sphere. The expression used for the build-up is strictly applicable for infinite medium but one is tempted to assume that it should be applicable to small organs situated inside the human body. Results obtained here also confirm that this assumption does not bring significant error and as such does not seriously limit the usefulness of the concept. Although the concept has been developed here for mono-energetic gamma radiation, it is a straightforward matter to extend it to any actual case, if the relative yields of γ rays of different energies are known, by calculating the geometric factor appropriate to each energy separately and weighing it by its fractional yield.

Acknowledgment

We are grateful to Col. S. K. Mazumdar, Director, Institute of Nuclear Medicine and Allied Sciences, for his keen interest and encouragement. Thanks are also due to Dr. A. K. Ganguly, Director, Chemical Group, BARC and Dr. D. V. Gopinath of Health Physics Division, BARC, Bombay for their comments.

REFERENCES

Berger, M. J., 1968. Energy deposition in water by photons from point isotropic sources. (MIRD Pamphlet No. 2), *Journal of Nuclear Medicine, Supplement Number 1*, 17–25.

Brownell, G. L., Ellett, W. H., and Reddy, A. R., 1968. Absorbed fractions for photon dosimetry. (MIRD Pamphlet No. 3), *Journal of Nuclear Medicine, Supplement No. 1*, 29–39.

Bush, F., 1949. The integral dose received from a uniformly distributed radioactive isotope. *British Journal of Radiology, 22*, 96–105.

Ellett, W. H., 1969. Application of gamma-ray diffusion theory to radiation dosimetry, Ph. D. Thesis, University of London.

Ellett, W. H., and Hume, R. M., 1971. Absorbed fractions for small volumes containing photon-emitting radioactivity. (MIRD Pamphlet No. 8), *Journal of Nuclear Medicine, Supplement Number 5*, 27–32.

Fitzgerald, J. J., Brownell, G. L., and Mahoney, F. J., 1967. In *Mathematical Theory of Radiation Dosimetry*, p. 332 (Gordon and Breach Science Publications, Inc., New York.

Focht, E. F., Quimby, E. H., and Gershowitz, M., 1965. Revised average geometric factor for cylinders in isotope dosage. Part I, *Radiology, 85*, 151–152.

Greenfield, M. A., and Lane, R. G., 1971. In *Radioisotope Dosimetry in Nuclear Medicine*, pp. 109 (W. H. Bland) (McGraw-Hill, New York).

Gupta, M. M., 1973. Some aspects of internal gamma-ray dosimetry, Ph. D. Thesis, University of Delhi.

Hubbard, L. B., and Williamson, F. S., 1969. Gamma-ray doses for all points in spheres and cylinders with uniformly distributed sources. *Physics in Medicine and Biology, 14*, 255–267.

Kovalev, F. E., 1958. The intensity of gamma radiation emitted by a cylindrical source. *International Journal of Applied Radiation and Isotopes, 3*, 113–118.

Loevinger, R., Holt, J. G., and Hine, G. J., 1956. Internally-administered radioisotopes. In *Radiation Dosimetry*, eds., G. J. Hine and G. L. Brownell (Academic Press, New York).

Loevinger, R., and Berman, M., 1968. A formalism for calculation of absorbed dose from radionuclides. *Physics in Medicine and Biology, 13*, 205–217.

Marinelli, L. D., Quimby, E. H., and Hine, G. J., 1948. Dosage determination with radioactive isotopes: II. Practical considerations in therap yand Protection. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 59*, 260–280.

Mayneord, W. V., 1945. Energy absorption: IV. The mathematical theory of integral dose in radium therapy. *British Journal of Radiology, 18*, 12–19.

Mayneord, W. V., 1950. Some applications of nuclear physics to medicine, *British Journal of Radiology, Supplement 2*, 171.

QUIMBY, E. H., FIETELBERG, S. and GROSS, W., 1970. In *Radioactive Nuclides in Medicine and Biology – Basic Physics and Instrumentation*, pp. 129, (Lea and Febiger, Philadelphia).

REDDY, A. R., ELLETT, W. H., and BROWNELL, G. L., 1967. Gamma-ray dosimetry of internal emitters: III Absorbed fractions of low energy gamma-rays. *British Journal of Radiology*, *40*, 512–515.

REDDY, A. R., GUPTA, M. M., and NAGARATNAM, A., 1971. Dosimetry of spherical sources (Abstract). III Annual Conference of the Society of Nuclear Medicine, India Varanasi.

SUNDARAN, V. K., GOPINATH, D. V., and GANGULY, A. K., 1965. Temperature distribution in gamma-active spheres. *Nuclear Structural Engineering*, *1*, 151–158.

TAYLOR, J. J., 1954. Application of gamma ray build-up data to shield design. WAPD–RM–217.

TRUCCO, E., 1964. Self-absorption in sphere and cylinders of radioactive material. *Bulletin of Mathematical Biophysics*, *26*, 303–307.

Book review

Positioning in Radiography. By K. C. Clark, 9th edn, Vols. 1 and 2, pp. 786, 1974 (Published for Ilfords Ltd. by William Heinemann Medical Books Ltd.), £15·00.

The compilers of the ninth edition of *Positioning in Radiography* have chosen to divide the subject-matter between two volumes so that "a more extensive coverage of each subject in both volumes has been possible". Writing as one who was brought up to believe that Miss Clark's book contained everything that one needed to know about radiographic technique, it is a little sad to find that these two volumes do not maintain that reputation. Some positioning has changed little or not at all, but modern apparatus and modern investigations have changed other radiographic techniques extensively, and it is obvious that the compilers are not always as familiar with new techniques as they should be. However, the high standard of presentation has been maintained, and some may think it has been enhanced by the addition of many new photographic illustrations, which will surely attract more males to the profession.

The principle of two volumes, one for general radiography and one for special techniques, is a good one, but I would query some of the decisions. For example, I would prefer Section 21 (temporal bones, optic foramina and additional views of the skull) to follow on from Section 9 (skull), since most of these views are carried out routinely, at least in larger departments; orthodontic techniques might be better included in the dental section while arthrography, expanded to include double contrast techniques, would seem more suitable for Volume 2.

Comparative exposure factors are always useful, but those given would have even more value if at least the type of generator used had been quoted, *e.g.* 2 pulse, 6 pulse, etc. Exposures for non-screen film used for extremities have been omitted, although this type of film is still used in many departments.

Unfortunately, too many of the radiographs used to illustrate technique are just not up to standard, faults including absence of markers, poor exposure factors, poor abdominal preparation, absence of lead protection and, in the angiographic section of Volume 2, poor radiological technique. There are also many instances in which the text does not agree with the photographic and/or the radiographic illustration. In particular, the photographs illustrating the technique for mammography will not provide good radiographs.

It is of course very difficult for a book of this kind to be kept up to date with advances in the equipment used for radiography. However, where new equipment affects the radiographic positioning used, it would be an advantage to include this, *e.g.* Mimer or Neurodiagnost and Orbix. There can be no excuse for the suggestion in the angiography section that the mA from one generator can be split between the two tubes in bi-plane angiography, since this practice was discarded many years ago due to the fact that the films were not of a sufficiently high standard.

Many of the sections are not in keeping with modern practice as previously stated, but it is impossible to detail all the parts that need reduction or enlargement. The following is only a sample with suggestions for improvement:

Special views of the skull: the section on the petrous bone would benefit from a more rational treatment. Very few ENT surgeons still require films of the mastoid tips or many views of the mastoid air cells, but do require further views of the middle ear (Mayers, Guillen and Chausée).

G.U. system: the description of IVU is inadequate; there is, for example, no mention of the danger of dehydrating patients in renal failure. Other additions could include advice on the technique and amount of contrast medium for renal failure; a better description of micturating cystograms recorded on video-tape or cine, and description of the technique for cyst puncture and nephrostogram. Angiography should be omitted from Volume 1.

G.I. system: additions should include double contrast techniques for the stomach, duodenum and colon.

Female reproductive system: 25 out of 30 pages are devoted to the pregnant abdomen. With the increase in the use of ultrasound, the need for radiography in pregnancy is diminishing, so perhaps a section could be added for ultrasound and more space given to gynaecography.

Angiography: this section is, I think, an absolute disaster. Ruthless pruning is needed of all the out-of-date material, better radiographs are required, and many techniques must be added, including venacavography and adrenal venography. The part on phlebography is particularly inadequate as is the part on renal angiography.

It would be better if, for future editions, radiographers who are expert in certain fields were invited to compile the specialist sections, since it is quite impossible for anyone else to provide the necessary detail and knowledge that comes from practical work in a specialist department. I am sure that if this is done Miss K. C. Clark will once more be on the pedestal where she belongs.

P. M. HOFFMAN.

1976, *British Journal of Radiology*, *49*, 76–80

Radiosensitization of C_3H mouse mammary tumours using fractionated doses of X rays with the drug Ro-07-0582

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(*Received May 1975 and in revised form July 1975*)

ABSTRACT

Three fractionated X-ray schedules were used, with and without the electron-affinic radiosensitizer of hypoxic cells, Ro-07-0582, to determine the local control of first-generation transplants of spontaneous mammary tumours in C_3H mice. Three or five fractions were given in either four or nine days overall time. The results were compared with acute skin reactions in other mice caused by the same treatment schedules. For a given skin reaction, the local control of tumours varied widely, from good to bad, when different X-ray only schedules were used. All three schedules using Ro-07-0582 however yielded good results. It appears that the use of the hypoxic-cell radiosensitizer took the unreliability out of these short fractionated treatments.

Electron-affinic drugs administered before X-ray treatment have been shown to enhance the radiosensitivity of hypoxic cells *in vitro* (Asquith *et al.*, 1974) and in solid tumours (Begg, Sheldon and Foster, 1974; Sheldon, Foster and Fowler, 1974). These drugs mimic the radiosensitizing effect of oxygen but diffuse more readily to the hypoxic cells because they are not so rapidly metabolized. The single X-ray dose required to cause a given response in solid tumours in mice was found to be reduced by factors of up to 2·2 by the drug 1-(2-hydroxy-3-methoxypropyl)-2-nitroimidazole (Ro-07-0582) in a number of murine tumours (Fowler and Adams, 1975; Denekamp and Harris, 1975). The "enhancement ratio" (ER) found for local control of first-generation tumour transplants in C_3H mice, as used in the present work, was 1·8 for the high drug dose of 1 mg/g bodyweight (Sheldon *et al.*, 1974).

When multiple doses of X rays are used to treat tumours, as in clinical radiotherapy, the net radiosensitization would be expected to be smaller than with single doses if physiological reoxygenation of the hypoxic cells in the tumour causes their number to be reduced during the course of the multi-fraction treatment. The present experiments were carried out in a tumour system known to be rapidly reoxygenating (Fowler *et al.*, 1972), in order to investigate whether any useful degree of radiosensitization was obtained with fractionated radiotherapy in such a tumour.

MATERIALS AND METHODS

First generation transplants of spontaneous mammary carcinomas were implanted subcutaneously on the anterior chest wall of C_3H mice from the Gray Laboratory inbred colony and used as described before. They were irradiated with 240 kV X rays (230 rads/minute; HVL 1·3 mm Cu) on reaching a mean diameter of $6{\cdot}5 \pm 1$ mm (Fowler *et al.*, 1974a). During irradiation mice were surrounded by oxygen at atmospheric pressure warmed to 25 ± 1°C in order to compare results with other work (Fowler *et al.*, 1972).

Mice receiving the drug Ro-07-0582 were injected intraperitoneally, 30 minutes before starting each of the irradiations, with 0·67 mg/g bodyweight of Ro-07-0582 dissolved in isotonic saline. All mice were anaesthetized with 60 mg/kg pentobarbitone sodium in isotonic saline injected intraperitoneally 15 minutes before starting the irradiations. The mice were given bemegride (Nicholas Products) (0·5 mg i.p.) after irradiation to aid resuscitation.

The fractionated treatments were given at corresponding times of day, usually in the morning. The mice were turned through 180 deg. halfway through each irradiation to ensure dose uniformity in the tumours.

Three fractionation schedules were used which had previously given good, mediocre and poor local control of tumours respectively for a given skin reaction caused by the same schedules in mice (Fowler *et al.*, 1974a); *i.e.* five fractions in nine days (5F/9d), three fractions in four days (3F/4d) and five fractions in four days (5F/4d).

After irradiation, tumours were measured at intervals of one or two weeks for 150 days from the mid-time of the irradiation. Any tumour growing to larger than 6 mm mean diameter was scored as a "recurrence". At 150 days, tumours under 4 mm in mean diameter were scored as "controlled". Those between 4 mm and 6 mm inclusive were scored as "ambiguous" and rejected from the analysis. Results were plotted as the proportion of tumours locally controlled for 150 days versus X-ray dose. The value of TCD 50 (dose required to control half the tumours) was computed as before using a program which also yields a best-fitting value for D_0', the inverse slope of the cell-survival curve required to fit the data (Porter and Peters private communication) and described by Fowler *et al.* (1974a). The values of D_0' are usually found to be several times larger than the cellular mean lethal doses, D_0, determined from *in vitro* or *in vivo* cell-survival curves, even if values of about $D_0 = 300$ rads for hypoxic cells are considered relevant. This is partly due to variable tumour size, to variations in the number of hypoxic cells in different tumours, and also to the use of multiple X-ray fractions.

For each fractionation schedule two such dose-response relationships were determined concurrently, one for the mice receiving Ro-07-0582 plus X rays and the other for the control group receiving X rays only. All the experiments were carried out on female mice, after July 1973, *i.e.* after the period of drift in tumour control doses described previously (Fowler *et al.*, 1975a; 1975b).

Although the dose-response relationships for acute skin reactions in the feet of WHT/Ht mice had previously been determined for the present X-ray schedules (Fowler *et al.*, 1974b), the schedules have recently been repeated with and without the drug (at the same concentrations), in order to test for the radiosensitizing potential of the drug Ro-07-0582 in normal tissue. These results are to be published in detail elsewhere (Foster, 1975), but the very small amounts of radiosensitization that were observed in the skin reactions have been taken into account in the present results, as described below.

RESULTS

Table I and Fig. 1 show the results for local tumour control at 150 days. Table II shows the fate of all the mice irradiated. The first three lines in Table II give the numbers of mice but the remainder of the table gives percentages. The number of mice lost from the experiments and therefore not analysed was significantly higher in the Ro-07-0582+X rays than in the X rays-only groups. This disparity occurred within the first week, after which the losses were evenly distributed. These early losses have been divided into three types:

(1) deaths at irradiation; believed to be due to a cumulative effect of Ro-07-0582 and anaesthetic on respiration;

(2) deaths occurring overnight after irradiation, although the mice had apparently recovered from the anaesthetic; and

(3) deaths due to the "0582 gut syndrome"; *i.e.* the stomach was very full of dry food whilst the rest of the gut was completely empty. The cause of this phenomenon is uncertain. Ro-07-0582 or a metabolite may inhibit either relaxation of the pyloric sphincter muscle or gastric secretion. It occurred in 15 per cent of the 5F/4d mice, usually on the fourth or fifth day after starting irradiation, but it did not occur in either the 3F/4d or 5F/9d régime. Therefore it seems to be related to daily dosage of the drug. The incidence of metastases did not appear to be influenced by the drug Ro-07-0582 (Table II).

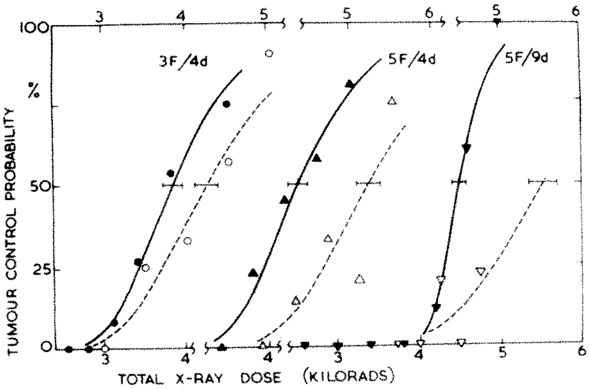

FIG. 1.

Tumour control probability versus total X-ray dose for the three fractionated schedules investigated. Full lines: Ro-07-0582 and X rays. Dashed lines: control X rays only. Error bars show standard errors of the mean TCD 50.

In the 5F/9d experiment the X-ray doses chosen were found to be too low (Fig. 1); this happened because the TCD 50 values for female mice had risen to equality with male mice since the previous experiments using this schedule (Fowler *et al.*, 1974a). The previously obtained TCD 50 for female mice, when multiplied by the appropriate correction factor of 1·28 to compensate for the male–female difference (Fowler *et al.*, 1974a; 1975a), was 5,430 rads, in remarkably close agreement with the present value of 5,480 rads. Even if the slope of the dose-response curve for 5F/9d treated with Ro-07-0582 and X rays was assumed to have a value of $D_0' = 850$ rads (obtained by averaging other experiments) instead of 280 rads, the resulting TCD 50 would still be significantly different from that for X rays only (see Table I).

It can be seen from Fig. 1 that a significant enhancement of tumour control occurred in the groups irradiated with the radiosensitizer. The effectiveness of radiosensitizers is usually defined in terms of the X-ray dose enhancement ratio, ER, which is the ratio of X-ray dose required to produce a given effect, say cure of 50 per cent of the mice with tumours, without radiosensitizers to the dose required *with* sensitizer. In this work the enhancement ratios found at the TCD 50 level were 1·11 ±

TABLE I

TUMOUR CONTROL RESULTS WITH AND WITHOUT THE RADIOSENSITIZER Ro-07-0582
TCD 50 is the X-ray dose required to control locally half the tumours at 150 days (rads ± 1 s.e.m.)

Schedule	X rays only			0582+X rays		
	Total rads	*Number controlled*	*Number analysed*	*Total rads*	*Number controlled*	*Number analysed*
3F/4d	3,000	0	12	2,550	0	8
	3,510	4	16	2,799	0	12
	4,020	4	14	3,099	1	12
	4,530	8	14	3,399	4	15
	5,040	10	11	3,801	7	13
				4,501	9	12
	TCD 50= 4,250 ± 140 rads D_0' = 780 rads			TCD 50= 3,830 ± 110 rads D_0' = 590 rads		
5F/4d	3,900	0	11	3,400	0	14
	4,300	2	14	3,800	3	13
	4,700	4	12	4,200	5	11
	5,100	2	10	4,600	7	12
	5,500	9	12	5,000	8	10
	TCD 50= 5,210 ± 140 rads D_0' = 780 rads			TCD 50= 4,360 ± 120 rads D_0' = 610 rads		
5F/9d	3,750	0	12	2,600	0	7
	4,000	0	14	3,000	0	12
	4,250	2	10	3,400	0	13
	4,500	0	13	3,800	0	13
	4,750	2	9	4,200	1	9
				4,600	6	10
				5,000	4	4
	TCD 50= 5,480 ± 170 rads D_0' = 850 rads Previously obtained TCD 50 for female mice × 1·28: 5,430 ± 200 rads			TCD 50= 4,510 ± 90 rads D_0' = 280 rads However if a D_0 value of 850 rads is assumed: TCD 50=4,890 ± 170 rads		

TABLE II

FATE OF THE IRRADIATED MICE

	3F/4d		5F/4d		5F/9d	
	X rays	0582	X rays	0582	X rays	0582
No. of mice irradiated	70	93	67	87	65	82
No. of mice analysed	67	72	59	60	58	68
No. of mice lost from experiment	3	21	8	27	7	14
% lost from experiment	4	23	12	31	11	17
Cause of losses: (%)						
Died at irradiation		2		5		9
Died overnight after irradiation		12		6		1
"0582 gut syndrome" (see text)				15		
Metastases	1		3	3	9	7
Gut injury		2*	1†			1‡
Marginal spontaneous tumours	3	2	1		2	
Ambiguous tumours at 150 days			3	2		
No. P.M. possible		4	3	1		

Days after starting irradiation: *=5 and 7 days
†=71 days
‡=10 days

0·05 s.e.m., 1·19±0·05 and 1·22±0·05 for the 3F/4d, 5F/4d and 5F/9d schedules respectively. These ERs are smaller than that of 1·8 previously found for single X-ray doses at the TCD 50 level using a larger drug dose of 1 mg/g bodyweight (Sheldon *et al.*, 1974). In order to compare the therapeutic effectiveness of the different schedules however, we have to assess the relative levels of injury to normal tissues. No complete data are yet available for any normal tissue except the skin of mice, although the present tumour control results can in future be reassessed as soon as data become available for other normal tissues.

The effect of the same three fractionation schedules using Ro-07-0582 and X rays on the skin reactions of WHT/Ht mice revealed no consistent enhancement of radiation effect. In two out of five experiments no enhancement was detected and in three a small ER, of less than 1·05, was seen over a range of mean acute skin reactions from about 0·8 to 1·8. These results will be published in detail elsewhere (Foster, 1975). It is clear that no significant enhancement occurred at average skin reactions of 1·5 for the fractionated schedules. However, an ER of about 1·15 was found for single X-ray doses. This probably corresponds to sensitization of the small proportion of hypoxic cells in skin that can be demonstrated when large single doses of X rays are used, as here (Withers, 1967). Therefore, the previously published fractionated X-ray doses required to yield this level of skin reaction (Fowler *et al.*, 1974b) could be used for the comparison, but the published single doses have to be divided by 1·15

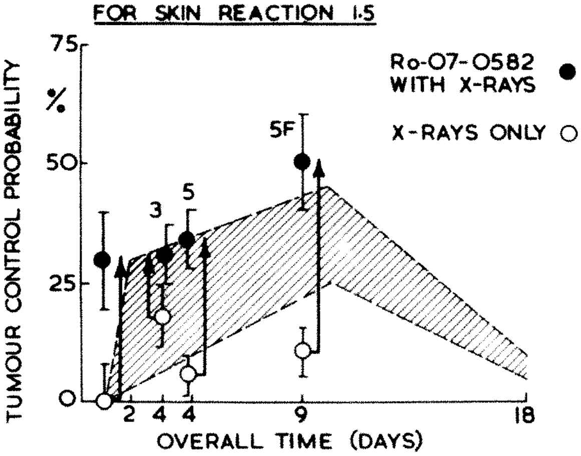

FIG. 2.

Tumour control probability for skin reactions of 1·5 versus overall time in days. The two left hand points are for single doses. Vertical arrows show the improvements in tumour control caused by use of the drug Ro-07-0582. The error bars are combined s.e.m.'s for both tumour control and skin reaction results. The result for single doses with Ro-07-0582 includes an allowance for an X-ray dose enhancement ratio of 1·15 for the skin reactions.

Tumour control probabilities at the X-ray doses which yielded skin reactions of 1·5 are shown in Fig. 2. A shaded area is also shown corresponding to the range of tumour control probabilities previously obtained with these and other fractionated X-ray schedules, all for skin reactions of 1·5 (Fowler *et al.*, 1974a; 1975a). In addition the corresponding results for single X-ray doses are shown, using the tumour control data from Sheldon *et al.* (1974) with an allowance made for the skin reaction ER of 1·15 for single doses mentioned above.

The vertical arrows in Fig. 2 indicate the extent of radiosensitization achieved by Ro-07-0582 plus X rays in this tumour system, for a standard skin reaction. All three fractionated schedules and the single doses were improved, so that they became near the upper border of the results obtained previously with the best X-ray only schedules.

Separate experiments were done to investigate the possibility of reduced serum concentrations of Ro-07-0582 which might arise if the repeated drug doses in these experiments induced the formation of enzymes which can rapidly destroy the drug. It was however found that the peak serum concentration was not significantly different after the fifth of five doses of 0·67 mg per gram bodyweight given in either four or nine days (Flockhart and Foster, 1975). It may therefore be concluded that the present ERs, either in tumours or skin, were not reduced by any such enzyme induction affecting drug concentrations.

DISCUSSION

All three fractionated schedules, and the single dose treatment, were improved by Ro-07-0582 so that they lay among the best results for tumour control found by any method of treatment (Fig. 2). This finding substantiates our previous claim that a small number of fractions given in a short overall time produced a low level of tumour control because of inadequate reoxygenation of the hypoxic cells in the tumours (Fowler *et al.*, 1974a).The drug Ro-07-0582 is unlikely to work by any processes other than by reducing the number of hypoxically radioresistant cells in the tumour, either by their radiosensitization or by a relatively small direct cytocidal effect (Sutherland *et al.*, 974).

The finding also demonstrates that the radiosensitizer is effective for multi-fraction schedules although less so for those that give good therapeutic results with X rays alone. The doses per fraction used here were quite large (800–1,400 rads) and the question remains open whether radiosensitization would also be obtained for schedules employing multiple small doses per fraction.

The present results are in close agreement with those of two-fraction and five-fraction experiments on regrowth delay in a transplanted murine carcinoma 'NT' recently carried out by Denekamp and Harris (1975).

Conclusions

Where short fractionated schedules using X rays alone may give highly variable results, due to finely balanced factors affecting reoxygenation (Fowler *et al.*, 1974a; 1975a), the use of the hypoxic-cell radiosensitizer Ro-07-0582 brings the effectiveness of all the schedules up to a good level, not significantly different from the best obtainable by other methods. Like fast neutrons (Fowler *et al.*, 1972), electron-affinic radiosensitizers seem to take the unreliability out of fractionated X-ray schedules.

Acknowledgments

The authors wish to thank Angela Walder, Ann Marriott and Jennifer Radmore for the breeding and care of the C_3H mice; Roche Products Ltd of Welwyn Garden City for the Ro-07-0582; Dr. E. H. Porter of the Glasgow Institute of Radiotherapeutics and Dr. L. J. Peters of the Gray Laboratory for the computer program used to calculate the TCD 50 values; Dr. G. E. Adams for encouragement; and the Cancer Research Campaign for support.

REFERENCES

Asquith, J. C., Watts, M. E., Patel, K., Smithen, C. E., and Adams, G. E., 1974. Electron-affinic radiosensitization: V. Radiosensitization of hypoxic bacteria and mammalian cells *in vitro* by some nitroimidazoles and nitropyrazoles. *Radiation Research*, *60*, 108–118.

Begg, A. C., Sheldon, P. W., and Foster, J. L., 1974. Demonstration of radiosensitization of hypoxic cells in solid tumours by metronidazole. *British Journal of Radiology*, *47*, 399–404.

Denekamp, J., and Harris, S. R., 1975. The response of a transplantable tumour to fractionated irradiation. Part I – X-rays and the electron-affinic radiosensitizer Ro-07-0582. (Submitted to Radiation Research).

Flockhart, I. R., and Foster, J. L., 1975. Species differences in the metabolism of a 2-nitroimidazole radiosensitizing drug: I. Serum levels and urinary excretion of the unchanged drug in mouse, dog, baboon and man. (To be submitted to *Xenobiotica*.)

Foster, J. L., 1975. Skin reactions in mice feet after X-irradiation with and without the radiosensitizer Ro-07-0582. (To be submitted to *International Journal of Radiation Biology*.)

Fowler, J. F., Denekamp, J., Page, A. L., Begg, A. C., Field, S. B., and Butler, K., 1972. Fractionation with X rays and neutrons in mice: response of skin and C_3H mammary tumours. *British Journal of Radiology*, *45*, 237–249.

Fowler, J. F., Denekamp, J., Sheldon, P. W., Smith, A. M., Begg, A. C., Harris, S. R., and Page, A. L., 1974a. Optimum fractionation in X-ray treatment of C_3H mouse mammary tumours. *British Journal of Radiology*, *47*, 781–789.

Fowler, J. F., Denekamp, J., Delapeyre, C., Harris, S. R., and Sheldon, P. W., 1974b. Skin reactions in mice after multifraction X-irradiation. *International Journal of Radiation Biology*, *25*, 213–223.

Fowler, J. F., and Adams, G. E., 1975. Radiosensitization of hypoxic cells in solid tumours in mice. *British Journal of Radiology*, *48*, 77–78 (abstract).

Fowler, J. F., Sheldon, P. W., Harris, S. R., Hill, S. A., and Ayres, S. E., 1975a. Relative effectiveness of 12-hourly fractionation and a non-uniform X-ray schedule in the optimum fractionation of C_3H mammary tumours. *British Journal of Radiology*, *48*, 581–589.

Fowler, J. F., Sheldon, P. W., Denekamp, J., and Field, S. B., 1975b. Optimum fractionation of the C_3H mouse mammary carcinoma using X-rays, the hypoxic cell radiosensitizer Ro-07-0582, or fast neutrons. *International Journal of Radiation Oncology, Biology and Physics*. (In press).

Sheldon, P. W., Foster, J. L., and Fowler, J. F., 1974. Radiosensitization of C_3H mouse mammary tumours by a 2-nitroimidazole. *British Journal of Cancer*, *30*, 560–565.

Sutherland, R. M., 1974. Chemotherapeutic effects of Flagyl (spheroid studies). Paper presented at the Workshop on Radiosensitization, Seattle, July 21st, 1974.

Withers, H. R., 1967. The effects of oxygen and anaesthesia on radiosensitivity *in vivo* of epithelial cells of mouse skin. *British Journal of Radiology*, *40*, 335–343.

1976, *British Journal of Radiology*, *49*, 81–83

Case reports

Neural arch dysplasia of the sixth cervical vertebra. "Congenital cervical spondylolisthesis"

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(Received March, 1975)

In 1951, Perlman and Hawes described a young man with pain and stiffness in the neck after a prolonged game of basketball in whom radiological examination showed a complex malformation of the posterior elements of the 6th cervical vertebra, associated with a Grade 1 spondylolisthesis; the authors described the condition as "cervical spondylolisthesis". Since their report, a further nine cases have been described (Kau, 1954; Schlüter, 1956; Lissner, 1956; Csakany and Almos, 1959; Solarino, 1961; Brocher, 1962; Niemeyer and Penning, 1963; Weidhopf, 1965), in addition to a similar malformation affecting the 4th cervical vertebra (Durbin, 1956), and a unilateral lesion, possibly a "forme fruste" (op den Orth, Penning and Kluft, 1969). Most of these authors also noted mal-alignment at the disc space below the affected vertebra, but Brocher (1962) suggested that this was a secondary phenomenon, and termed the anomaly "neural arch dysplasia" (Bogendysplasie); Csakany and Almos (1959) proposed the title "C6 symptom-complex" in view of the constant level of affection.

The present report is the first in the British radiological literature.

Case history

A 14-year-old boy was seen at the Royal National Orthopaedic Hospital, having injured his neck in a fall two weeks previously, and again on the day of admission. Examination showed marked torticollis, tenderness of the spines of the 3rd and 4th cervical vertebrae, and reduced neck flexion; there were no neurological signs. Next day the signs and symptoms had cleared; the patient was discharged and has remained symptom-free.

Radiological examination showed abnormalities involving mainly the 5th and 6th cervical vertebrae, particularly the latter (Fig. 1). The neural arches were reduced in height, and the normal obliquity of the posterior intervertebral joints was decreased. The spines of both vertebrae were well developed, but unfused in the midline. The bodies were also lacking in height, and there was anterior displacement of about 5 mm of the 6th vertebra on the 7th. Probable defects were seen running across the pars interarticularis. There was a right cervical rib, and a well-developed ponticulus posticus. Flexion and extension views showed only limited movement of the lower cervical spine.

DISCUSSION

The typical features of this condition are as follows:

(1) Clinical: All but one of the patients have been male (Brocher, 1962). The presentation has been very varied, but most patients have complained of neck, arm or shoulder pain of very variable duration. A definite history of trauma has commonly been lacking. Physical examination has been negative, or shown local tenderness; neurological signs have always been absent.

(2) Radiological: The basic abnormality is a dysplasia of the posterior elements of the 6th cervical vertebra, manifest as:

(a) Spina bifida. Only the otherwise atypical cases of Durbin (1956) and op den Orth *et al.* (1969) lacked this feature. More than one level may be involved, as in the present case, and those of Brocher (1962) and Schlüter (1962). This dysraphism has not been associated with external stigmata.

(b) Spondylolysis. A break in the pars interarticularis on one (op den Orth *et al.* 1969) or both sides has been an almost constant feature, although Perlman and Hawes (1951) described merely "extreme thinning" of this structure.

(c) Affection of the posterior intervertebral joints. Abnormal inclination of the superior and inferior articular factes of the affected bones has often been associated with hypertrophy of the adjacent articular processes, particularly those of the 7th vertebra. In three cases: those of Lissner (1956), Brocher (1962) and the present case, the joints of the 5th vertebra were also dysplastic.

The most common associated abnormality is forward slip, usually of not more than 3–4 mm, of the 6th on the 7th cervical vertebrae; only the unilateral lesion described by op den Orth *et al.* (1969) did not show this. Whether this is a result of the break in the pars, or of the joint dysplasia, or both, is not clear. In the present patient, as in that of Niemeyer and Penning (1962), no instability was shown, although Kau (1954) and Durbin (1956) found the

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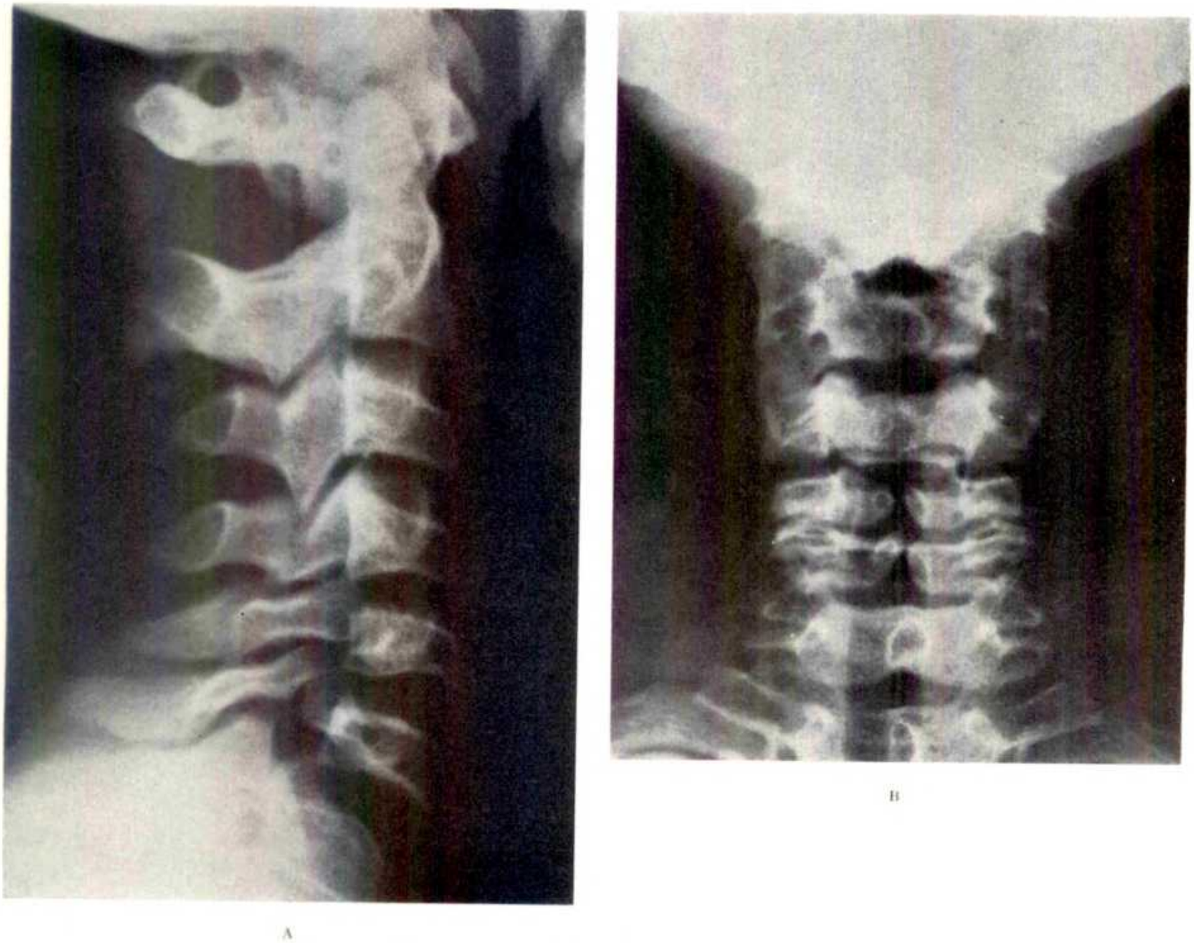


FIG. 1.

Cervical spine.

(A) lateral projection. The bodies and neural arches of C5 and C6 are lacking in height, and the latter are deformed. The cortical line at the base of the spinous processes is missing, indicating spina bifida. A well-corticated break in the pars interarticularis is seen at C6 (there is a possible break at C5), and there is a 5 mm forward slip of C6 on C7. C1 has a well-developed ponticulus posticus.

(B) antero-posterior projection. The shallow neural arches of C5 and C6 are clearly seen, as is the spina bifida. There is a cervical rib on the right.

slip to be completely reduced in flexion and in extension respectively; Csakany and Almos (1959) noted that the pars defect became more obvious in flexion, but did not comment on the spondylolisthesis.

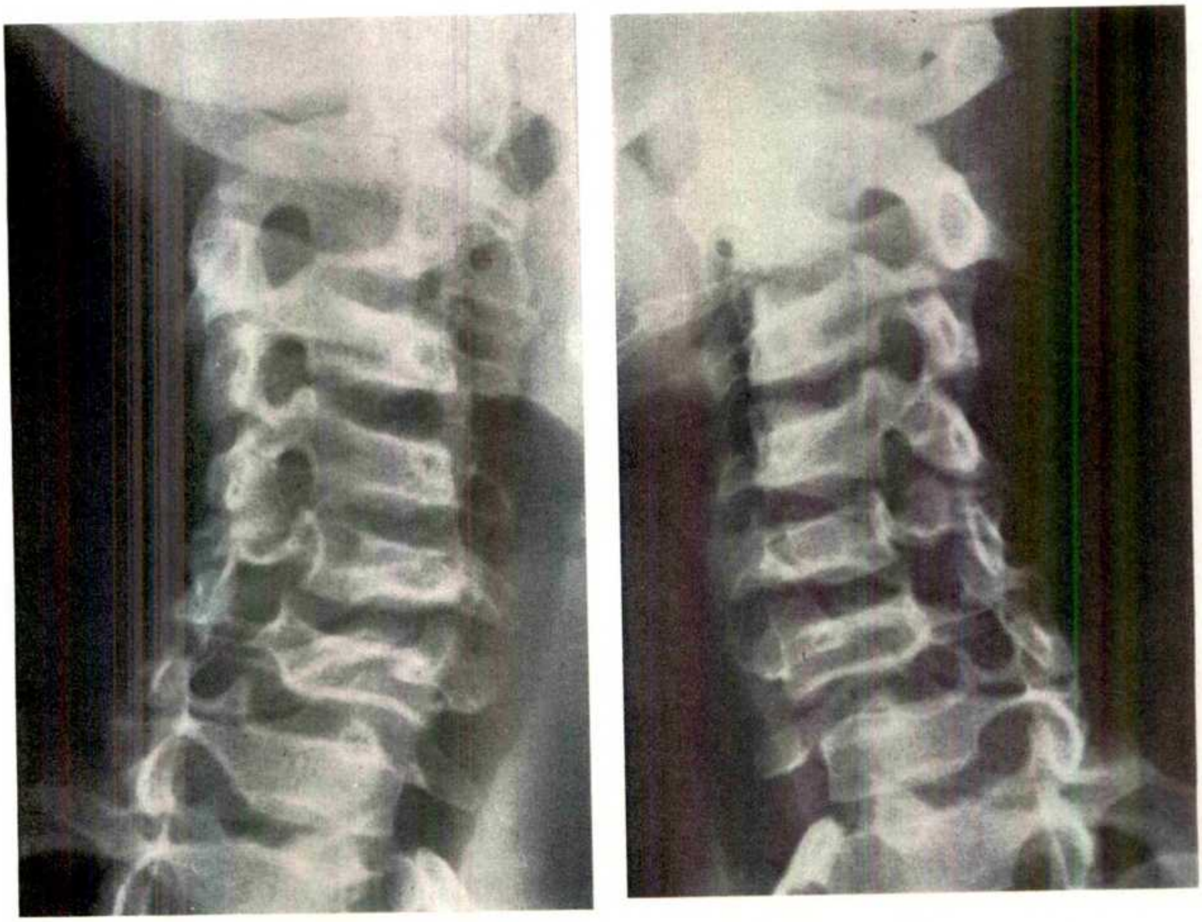
Several patients (Kau, 1954; Durbin, 1956) showed, like the present case, unequivocal deformity of the affected vertebral bodies. The present report is the first including a cervical rib, although Widhopf (1965) did comment on a "persistent apophysis on the transverse process of the first thoracic vertebra".

Although this lesion is clearly congenital in origin, its relationship to trauma is not clear. Most of the patients have not given a clear history of injury, but several were, for example, labourers, in whom chronic minor neck trauma could not be excluded. In the patient seen by op den Orth *et al.* (1969) only four days after acute trauma, the break in the pars interarticularis was nevertheless well corticated.

This dysplasia would thus seem to be an incidental finding in the majority of cases, but represents an anomaly with which the radiologist should be familiar.

ACKNOWLEDGMENTS

I should like to thank Mr. E. L. Trickey, for permission to publish details of his patient; Miss E. M. Manhire for drawing the case to my attention; Dr. Wilhelm Radü for



C

D

Fig. 1.
Cervical spine
(C) and (D) oblique projections. The dysplastic neural arches are well seen.

assistance with translation; and the Medical Photographic Department of the Institute of Orthopaedics at Stanmore for the preparation of the illustrations.

REFERENCES

BROCHER, J. E. W., 1962. *Die Wirbelsaulenleiden und ihre Differentialdiagnose*. (Thieme, Stuttgart).

CSAKANY, G., and ALMOS, S., 1959. Echte Spondylolisthese der Halswirbelsäule (C6-Symptomenkomplex). *Fortschritte auf dem Gebeite der Röntgenstrahlen*, *91*, 277–280.

DURBIN, F. C., 1956. Spondylolisthesis of the cervical spine. *Journal of Bone and Joint Surgery*, *38B*, 734–735.

KAU, R., 1954. Spondylolisthesis der Halswirbelsäule. *Archiv für orthopaedische und Unfall-Chirugie*, *46*, 502–507.

LISSNER, J., 1956. Spondylolisthese der Halswirbelsäule. *Fortschritte auf dem Gebeite der Röntgenstrahlen*, *84*, 626–628.

NIEMEYER, T., and PENNING, L., 1963. Functional roentgenographic examination in a case of cervical spondylolisthesis. *Journal of Bone and Joint Surgery*, *45A*, 1671–1678.

OP DEN ORTH, J. O., PENNING, L., and KLUFT, O., 1969. Lateral spondylolysis of the sixth cervical vertebra. *Journal of Bone and Joint Surgery*, *51A*, 1379–1382.

PERLMAN, R., and HAWES, L. E., 1951. Cervical spondylolisthesis. *Journal of Bone and Joint Surgery*, *33A*, 1012–1013.

SCHLÜTER, K., 1956. Ueber Spondylolisthesis der Halswirbelsäule. *Medizinische Klinik*, *51*, 1018–1021.

SOLARINO, G. B., 1961. Über eine seltene Dysplasie an der Halswirbelsäule. *Schweizerische Medizinische Wochenschrift*, *91*, 1493–1494.

WEIDHOPF, H., 1965. Über die Spondylolisthesis im Halsbereich. *Beitrage zur Orthopaedie und Traumatologie*, *12*, 694–696.

1976, *British Journal of Radiology*, *49*, 84–86

Case reports

Primary malignant nodule. Variation in size with pulmonary venous pressure

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(*Received July 1975*).

Primary lung carcinoma, presenting as a solitary pulmonary nodule, increases in size when examined over a period of time; rarely it may remain static, Steele (1967), Good (1963), Davis, Peabody and Katz (1956).

The case presented demonstrated significant reduction in size of a solitary pulmonary nodule on two occasions. Subsequently the lesion was shown to be a primary squamous-cell carcinoma. No similar case has been traced in the literature.

Case history

A 55-year-old man was found to be diabetic ten years previously. Chest X ray at that time showed calcified tuberculous lesions at the left apex and right hilar calcification, but no other abnormality.

The recent history was of congestive cardiac failure. Chest X ray on admission showed cardiomegaly, upper zone blood diversion and a large right pleural effusion. The tuberculous lesions at the left apex were unchanged.

After five days of treatment a repeat chest X ray showed that the right pleural effusion had decreased in size to reveal a 2 cm rounded opacity in the right mid zone (Fig. 1). Sputum cytology and culture were negative for malignant cells and tuberculosis respectively. A diagnostic pleural tap showed xanthochromic fluid with no evidence of malignant cells. The nodule at this time was thought to be a tuberculoma or bronchial carcinoma, and it was decided to observe its progress.

A further chest X ray four months later showed the opacity to be smaller, having a diameter of 1·5 cm. The pleural fluid had cleared and cardiac size was normal (Fig. 2).

Six months later the nodule had increased in diameter to 2 cm.

One year after his original admission, the patient again went into congestive cardiac failure. Chest X ray showed cardiomegaly, upper zone blood diversion and a return of a right sided pleural effusion. The nodule was now oval and

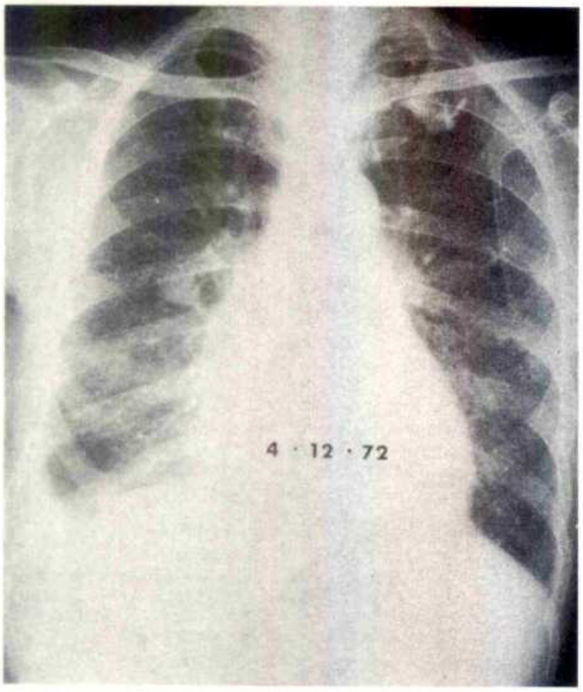

FIG. 1.

December 4, 1972. Following reduction in size of the pleural effusion, a nodule is seen in the right mid zone, diameter 2 cm.

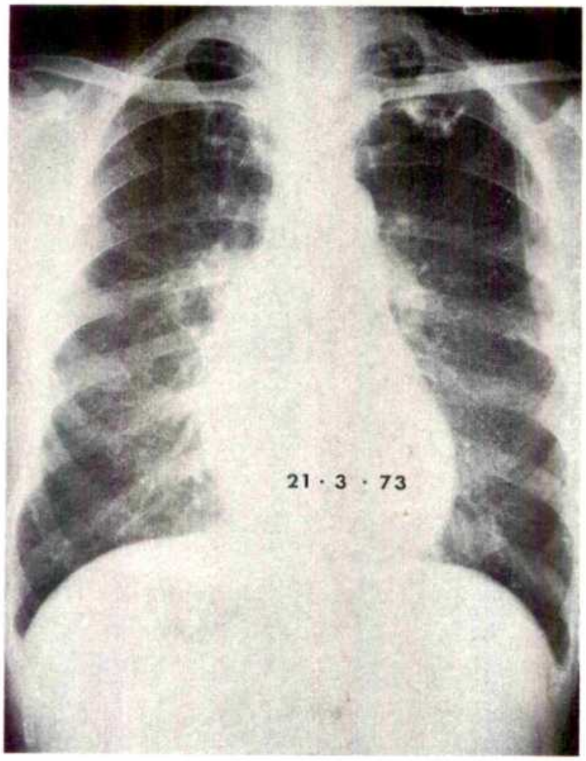

FIG. 2.

March 21, 1973. Heart size is now normal and the pleural fluid has absorbed. Nodule is less well defined. Maximum dimension 1·5 cm.

measured 4·5 by 3 cm (Fig. 3). With treatment the patient improved and a repeat chest X ray six days later showed a reduction in cardiac size and in the amount of the pleural fluid. There was a concomitant reduction in size of the nodule to 3 by 2 cm (Fig. 4). Sputum cytology was again negative for malignant cells, and culture showed no growth of tubercle bacilli. Needle biopsy of the lesion showed clumps of squamous cell carcinoma and these findings were confirmed after right upper lobectomy. Examination of the specimen showed a poorly differentiated squamous cell carcinoma arising from the proximal part of the posterior segmental bronchus. There was no evidence of any other pathology in or around the lesion. The bronchial stump was free of tumour tissue.

DISCUSSION

Few authors, *e.g.* Nathan (1974) would advocate a policy of observation for a newly-discovered solitary pulmonary nodule of uncertain aetiology. Where such a lesion has been inadvertently observed for some time, however, comparison with previous films may be invaluable. Many authors have stressed the importance of an increase in size as a diagnostic feature of malignancy. Rarely such lesions may remain static.

Steele (1963) and Good (1963) consider that failure to grow over a two-year period makes it highly unlikely that a nodule is malignant, while Davis *et al.* (1956), would prefer a five-year period before deciding against an exploratory thoracotomy for a doubtful lesion. No published report of a primary malignant nodule showing a spontaneous decrease in size has been traced in the English literature.

In this case all the films illustrated were taken using standard postero-anterior projection with a target to film distance of 6 ft. Significant variation in size due to radiographic factors can therefore be discounted.

The nodule showed a reduction in size on two occasions. In the first instance this occurred over a period of 15 weeks, and in the second over six days. The size of the nodule correlates well with clinical and radiological evidence of changes in pulmonary venous pressure, the nodule enlarging when the patient went into congestive cardiac failure and increasing when his condition improved.

In view of this, and of the speed with which the nodule reduced in size on the second occasion, it is asserted that a causal relationship exists between nodule size and pulmonary venous pressure. The precise mechanism involved is uncertain. Nodules in this situation drain via the pulmonary venous system

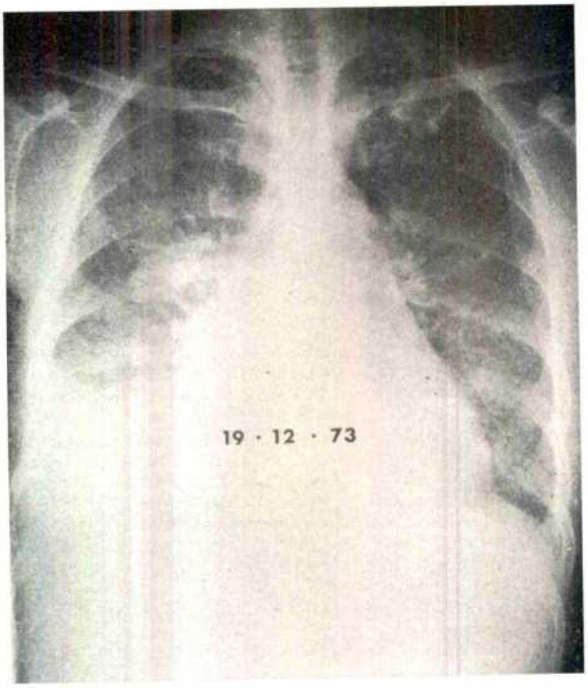

FIG. 3.

December 19, 1973. Cardiomegaly and effusion again present. The nodule is oval and measures 4·5 by 3 cm.

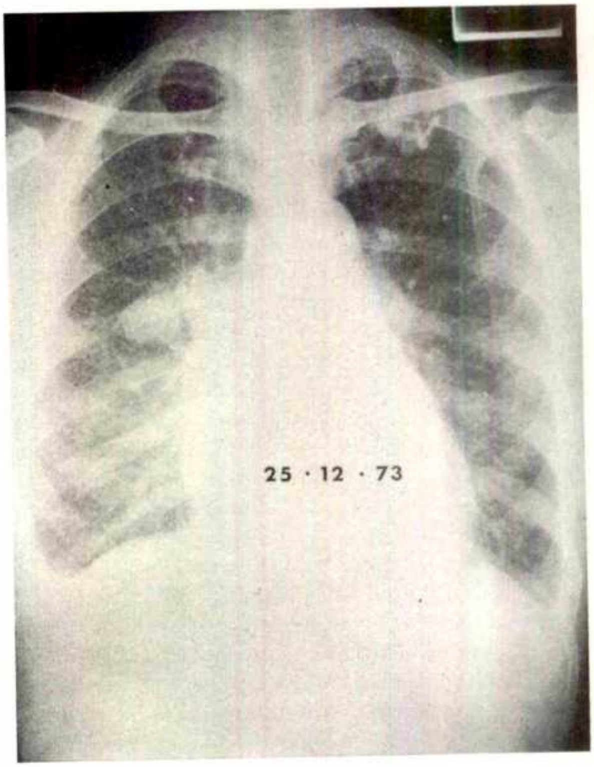

FIG. 4.

December 25, 1973. Following improvement in heart failure the nodule is smaller and measures 3 by 2 cm.

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and the changes in size presumably reflect the accumulation and subsequent dispersal of fluid in or around the lesion consequent on changes in pulmonary venous pressure. In this context it is important to note that the resected specimen showed the tumour itself but no evidence of other pathology; in particular there was no evidence of associated collapse or consolidation distal to the lesion.

SUMMARY

A squamous-cell carcinoma presenting as a solitary pulmonary nodule in a patient with congestive cardiac failure is described. Significant changes in size of the nodule were observed to correlate well with clinical and radiological evidence of changes in pulmonary venous pressure. It is suggested that the relationship is causal, with fluid accumulating in or around the nodule when the venous pressure rises and subsequently dispersing when the pressure falls.

ACKNOWLEDGEMENT

We wish to thank Dr. J. C. Batten, Physician to St. George's Hospital, for granting permission to record the case report, to Miss Underhill, Medical Photographer, to radiographic staff at St. George's Hospital, and to Miss Margaret Sabin for secretarial assistance.

REFERENCES

DAVIS, E. W., PEABODY, J. W. Jnr., and KATZ, S. 1956. Solitary pulmonary nodule: ten year study based on 215 cases. *Journal of Thoracic Surgery*, *32*, 728–771.

GOOD, C. A., 1963. Solitary pulmonary nodule. A problem in management. *R.C.N.A.*, *1*, 429–443.

NATHAN, M. H. 1974. Management of solitary pulmonary nodules. An organized approach based on growth rate and statistics. *J.A.M.A.*, *227*, 1141–1144,

STEELE, J. D., 1963. The solitary pulmonary nodule. Report of a co-operative study of resected asymptomatic solitary pulmonary nodules in males. *Journal of Thoracic and Cardiological Surgery*, *46*, 21.

1967. The solitary pulmonary nodule. *University of Michigan Medical Centre Journal*, *33*, 54–57.

The computed axial tomograph in acute herpes simplex encephalitis

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(*Received June, 1975*)

If there is to be any benefit from the treatment of herpes simplex encephalitis, diagnosis must be made early on in the disease, possibly even within the first 48 hours. A major difficulty arises because many of the patients do not develop symptoms and signs severe enough at an early stage to warrant a brain biopsy, which is often the only method of establishing a definite diagnosis. By this method the virus can usually be recognized by immunofluorescence studies, electron microscopy or virus culture. Prior to this the presence of a sterile lymphocytosis in the cerebrospinal fluid and slow wave activity on the EEG with increased spikes may suggest the diagnosis, and special radiological studies may be of considerable further assistance.

A recent paper by Pexman (1974) described the angiographic and brain-scan features of acute herpes simplex encephalitis, from a survey of 11 cases, in which a characteristic picture of a temporal lobe mass with persistent filling of some terminal arteries, local areas of hypervascularity, staining or blush, and early venous drainage was found with the former investigation, and a wedge-shaped area of abnormal uptake in the anterior view in the latter, from the fifth day of the illness onwards. In Bristol, we recently investigated a case of herpes simplex encephalitis with the EMI scanner as well as a brain scan, and as the appearances in the former were thought to be typical of the disease, it might be valuable for other centres, particularly those with access to a scanner, to be aware of the potential of this technique.

Case history

The patient was a female student nurse aged 20 years, who, previously healthy, developed a flu-like illness with a sore throat and headaches, followed seven days later by neck stiffness. Later that day she became drowsy and confused with a temperature of 38°C. A lumbar puncture at that time showed a pressure of 130 mm, 150 WBC mostly lymphocytes per mm^3 and a sugar of 80 mg/per cent, findings which were interpreted as an aseptic meningitis.

The following day she developed photophobia and started to vomit, becoming more confused and disorientated, with the onset of focal fits involving mainly the right side of the face. She developed an infection in the right lung, and eventually a tracheostomy tube was inserted. She was transferred to the Regional Neurological Unit under the care of Dr. M. J. Campbell on the 14th day of her illness, deeply unconscious, with focal fits and unreactive pupils. On the same day she had a linear isotope scan and an EMI scan of her brain (Fig. 1). The first showed a wedge-like uptake in the left temporal region extending to the lateral margin of the brain in the antero-posterior view similar to

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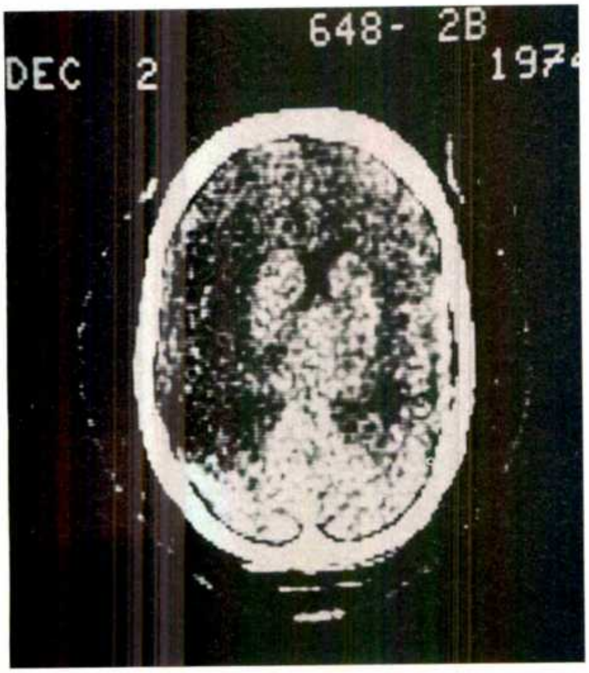

FIG. 1.

EMI scan taken on 14th day of illness showing normal-sized ventricles with a slight shift of the septum pellucidum to the right of the midline.

those described by Pexman, and the latter showed normal-sized ventricles, with a slight shift of the septum pellucidum to the right of the midline, together with areas of low absorption coefficient in both temporal lobes more marked on the left, and extending into the frontal and parietal regions, interpreted as areas of encephalitis. In view of the typical distribution the appearances were thought to be characteristic of a herpes simplex infection. This was confirmed by brain biopsy later the same day (Mr. Huw Griffith). The brain was found to be tight and bulging and the cortex was red. Dr. D. M. Brownell reported the smear as showing an oedematous white matter with considerable fresh haemorrhage, and infiltrate of inflammatory cells consistent with encephalitis. Dr. A. Clark reported that fluorescent antibody preparations gave a positive result for herpes simplex virus, and in addition herpes simplex virus was isolated from the brain tissue after 24 hours, and also from the throat swab. She was treated with Cytosine Arabinoside and steroids and nursed in the ICU but deterioration continued, with death occurring five days after admission. A brain section after fixation, in the same plane as the EMI scan confirmed the ventricular shift to the right and the widespread swelling and haemorrhagic softenings in both temporal lobes, particularly on the left. Histology confirmed the changes of acute encephalitis.

COMMENT

In Pexman's series, positive findings at angiography were noted in cases investigated between the 5th and 21st day after the onset of the illness, and the brain scans, carried out between the 8th and 21st day, were all positive. Our investigations were carried out on the 14th day of the illness, but it seems very likely that the EMI scan might well be positive if carried out much earlier than that.

REFERENCE

PEXMAN, K. H. W., 1974. The angiographic and brain scan features of acute herpes simplex encephalitis. *British Journal of Radiology*, *47*, 179–184.

Granular cell myoblastoma of the bronchus

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(*Received March, 1975*)

Granular cell myoblastoma is a relatively uncommon lesion of disputed histogenesis which is seen most frequently in the subcutaneous tissues and in the tongue (Strong, McDivitt and Brasfield, 1970). It rarely occurs in the bronchus; Weitzner and Oser in a search of the literature could only find 30 cases to which they added one of their own.

Many authors have discussed the origin and nature of the lesion, some regarding it as non-neoplastic, either a degenerative reaction (Ewing, 1940; Willis, 1960) or a storage disorder (Azzopardi, 1956; Shear, 1960), but most regarding it as neoplastic. However, the latter disagree on the cellular origin of the neoplasm, the suggestions being neural (Ashburn and Rodger, 1952; Fisher and Wechsler, 1962), myogenic (Murphy, Dockerty and Broders, 1949), fibroblastic (Pearse, 1950) and mesenchymal (Toto and Restarski, 1967).

Reviewing the available evidence and adding evidence of their own from electron microscopic studies, Garancis, Komorowski and Kuzma (1970) have favoured an origin from the Schwann cell and this remains the most popular hypothesis.

In view of the rarity of the lesion in the bronchus we would like to discuss briefly the rather unusual bronchographic appearances.

Case History

A nurse aged 40 years, had been in good health until 1970, three years before admission. Over this three-year period she had experienced attacks of increased cough with colourless sputum. During one of these attacks in October 1972, some linear atelectasis in the left upper lobe was detected on chest X ray. Two months later this had cleared completely only to reappear in exactly the same situation during a subsequent exacerbation of symptoms in April 1973. On this occasion, there was also a small dense shadow close to the upper pole of the left hilum (Fig. 1). A left bronchogram at this stage showed a flattened filling defect in the anterior segmental bronchus of the left upper lobe (Figs. 2 and 3).

She was admitted for surgery in July, 1973. On examination she was a fit-looking, slightly overweight woman with no abnormal physical signs in the respiratory system. Haematology was normal and sputum cytology showed no malignant cells. Bronchoscopy with a rigid bronchoscope was normal and repeat bronchogram showed the same features as before.

At left thoracotomy, the pleura was free and the left upper lobe appeared normal, but a nodular mass was found in association with the left upper lobe bronchus. A left upper lobectomy was performed and on opening the bronchus a smooth, rounded tumour 2·1 × 1·8 cm was seen projecting into the lumen of the anterior segmental bronchus, reducing its lumen by about 50 per cent.

Histological examination revealed a well-circumscribed lesion pressing into the bronchus covered by intact bronchial epithelium and not arising therefrom (Fig. 4). It was composed of rather uniform elongated large cells (Fig. 5) with moderately eosinophilic granular cytoplasm and somewhat indistinct boundaries. The nuclei were large with a tendency to elongation but nucleoli on the whole were not conspicuous and mitotic figures were not a feature. The granules were rather weakly PAS-positive and their diastase resistance equivocal but the appearances were considered those of granular cell myoblastoma.

The patient's convalescence was uneventful and one year later she remains well with no evidence of recurrence or the development of fresh lesions elsewhere.

DISCUSSION

By comparison with the cases reviewed by Weitzner and Oser (1968), our case appears typical in age group, clinical presentation and situation. In their

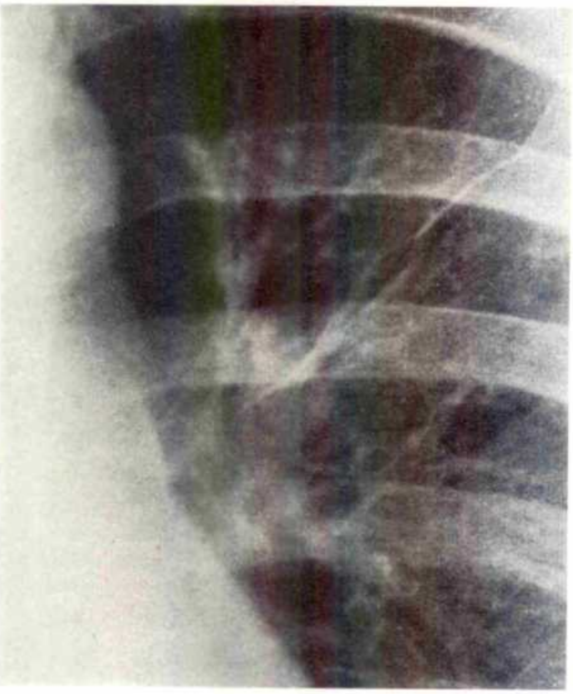

FIG. 1.

Detail of postero-anterior chest radiograph showing linear atelectasis and small mass adjacent to the left hilum.

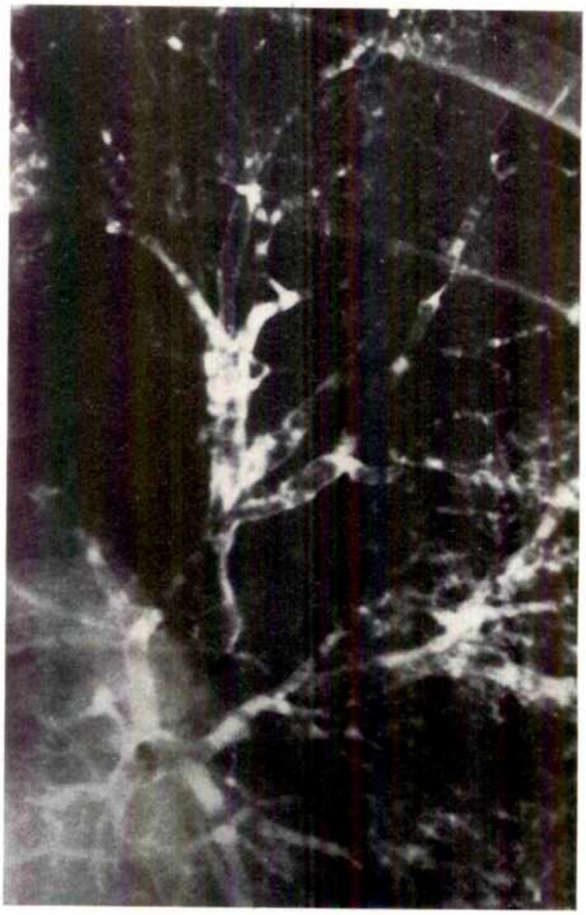

FIG. 2.

Left bronchogram showing smooth-filling defect in anterior segmental bronchus of the left upper lobe.

series the lesion presented most frequently in the fourth and fifth decades of life with a history of "repeated pulmonary infection" in one-third of cases and was twice as frequent in the upper lobes as in the lower lobes. However, in only two out of 31 cases did the lesion occur in a segmental bronchus; the lobar bronchi, main bronchi and trachea were the usual sites.

In the case reported here, the relatively long history with very slow progression of X-ray changes suggested a benign lesion but a histological diagnosis was not made pre-operatively as the lesion was not seen at bronchoscopy.

The bronchographic appearances of localized narrowing of a bronchus is unusual in neoplastic disease of the lung. A primary carcinoma nearly always completely occludes the bronchus before producing symptoms; it then grows through the bronchial wall and its proximal extension compresses the bronchus externally to produce the characteristic "rat-tailed" narrowing. A bronchial adenoma most frequently produces a rounded blunt obstruction of a bronchus indistinguishable from a carcinoma. However, in about one-third of cases it widens the lumen proximal to the obstruction by growing entirely within the bronchus and stretching its wall. This so-called "wide-lumen sign" is almost pathognomonic of bronchial adenoma (Nelson and Christoforodis, 1973). Granular cell myoblastoma is a slow-growing submucosal lesion which enlarges submucosally often without breaching the mucosa, giving rise to a localized smooth-filling defect.

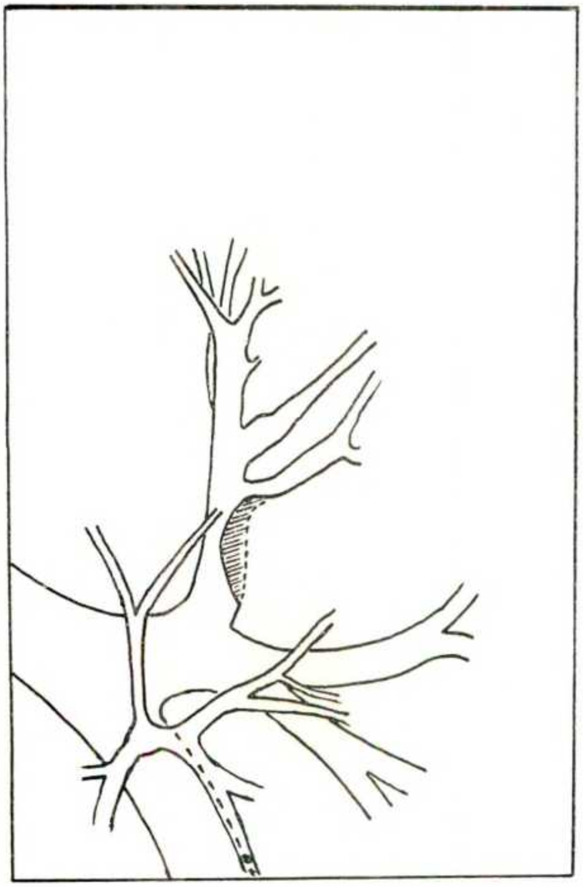

FIG. 3.

Diagram of left bronchogram to show extent of filling defect (hatched area).

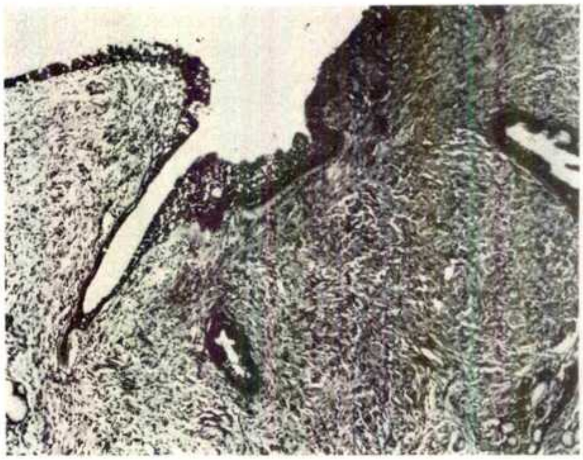

FIG. 4.

Intact bronchial epithelium covering the lesion (original magnification ×13).

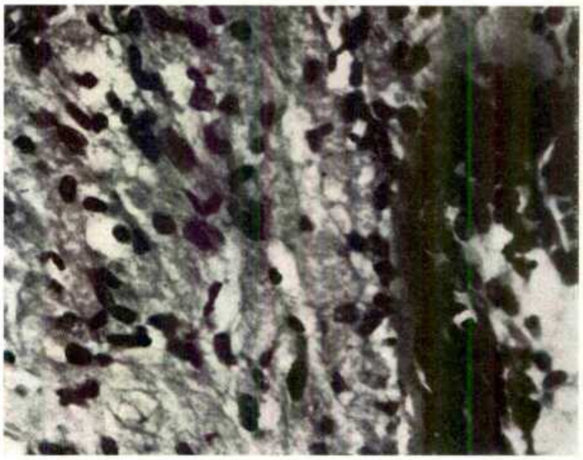

FIG. 5.

Elongated large cells with granular cytoplasm and large, rather elongated nuclei (original magnification ×130).

Localized bronchographic filling defects may be artefactual due to bubbles or mucus; these are not consistent from film to film. Smooth concentric narrowing may be due to local bronchial spasm, particularly in patients with asthma or chronic bronchitis. Other benign conditions to be considered in the differential diagnosis of a localized filling defect are fibrosis secondary to tuberculous endobronchitis and sarcoidosis (Simon, 1971).

Localized smooth bronchial narrowing cannot, therefore, be regarded as pathognomonic of the very rare granular cell myoblastoma, but is nearly always associated with a benign lesion.

Although fibre-optic bronchoscopy, bronchial brushing techniques under fluoroscopy and high-speed drill biopsy are all becoming fashionable, it is felt that bronchography, by demonstrating characteristic filling defects, can still play an important part in establishing the diagnosis.

REFERENCES

Ashburn, L. L., and Rodger, R. C., 1952. Myoblastomas. Neural origin. *American Journal of Clinical Pathology*, *22*, 440–448.

Azzopardi, J. G., 1956. Histogenesis of the granular cell "myoblastoma". *Journal of Pathology and Bacteriology*, *71*, 85–94.

Ewing, J., 1940. In *Neoplastic Diseases*, 4th edn., pp. 247–248 (W. B. Saunders and Co., Philadelphia).

Fisher, E. R., and Wechsler, H., 1962. Granular cell myoblastoma—a misnomer. *Cancer*, *15*, 936–943.

Garancis, J. C., Komorowski, M. D., and Kuzma, J. F., 1970. Granular cell myoblastoma. *Cancer*, *25*, 542–550.

Murphy, G. H., Dockerty, M. D., and Broders, A. C., 1949. Myoblastoma. *American Journal of Pathology*, *25*, 1157–1178.

Nelson, S. W., and Christoforodis, A. J., 1973. Bronchography in disease of the adult chest. *Radiological Clinics of North America*, *11*, 125–151.

Pearse, A. G., 1950. The histogenesis of granular cell myoblastoma (granular cell perineural fibroblastoma). *Journal of Pathology and Bacteriology*, *62*, 351–362.

Shear, M., 1960. The histogenesis of the so-called "granular cell myoblastoma". *Journal of Pathology and Bacteriology*, *80*, 225–228.

Simon, G., 1971. In *Principles of Chest X-ray Diagnosis*, 3rd edn., pp. 223 (Butterworths, London).

Strong, E. W., McDivitt, R. W., and Brasfield, R. D., 1970. Granular cell myoblastoma. *Cancer*, *25*, 415–422.

Toto, P. D., and Restarski, J., 1967. Histogenesis of the granular cell myoblastoma. *Oral Surgery*, *24*, 384–387.

Weitzner, S., and Oser, J. F., 1968. Granular cell myoblastoma of the bronchus. *American Review of Respiratory Disease*, *97*, 923–929.

Willis, R. A., 1960. In *Pathology of Tumours*, 3rd edn., pp. 747–751 (Butterworths, Washington, D.C.).

The double pylorus

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(*Received April, 1975*)

The double pyloric channel has been described as a rare malformation which in the past has been considered congenital (Christien *et al.*, 1971).

In recent years, however, some case reports have indicated that this lesion may be acquired (Hansen Kronborg and Pedersen, 1972; Drapkin *et al.*, 1974; Farack *et al.*, 1974). Since, to our knowledge, no reports on this matter have yet appeared in the radiological literature, we feel it important to publish our case.

Case history

A 43-year-old man with a 20-year history of upper abdominal discomfort was admitted to the Department of Surgery, Glostrup Hospital, Copenhagen. His pains were worse before meals, and relieved on taking food. They were associated with nausea, heartburn and occasional vomiting. There was no history of melaena.

Ten months previously he had been admitted to the Department of Medicine with severe melaena, anaemia (Haemoglobin 6·7 g per 100 ml.) and pronounced upper abdominal pains. Upper gastro-intestinal X-ray studies revealed a prepyloric ulcer on the lesser curvature of the stomach (Fig. 1). Other laboratory findings at that time were normal, particularly bleeding and coagulation times. Following transfusion the patient recovered. Gastroscopy revealed a healing ulcer without any suspicion of malignancy. He was discharged from the hospital shortly afterwords on a diet and antacids.

On admission laboratory investigations were normal, and at gastroscopy no ulcer or other abnormalities were found in the prepyloric region. However, a barium meal showed a normal pylorus coexisting with a narrow fistula between the prepyloric part of the stomach and the bulb of the duodenum (Fig. 2). No operative treatment was instituted and the patient was discharged from hospital.

DISCUSSION

These findings demonstrate conclusively that double pylorus or more correctly expressed, gastro-duodenal fistula in the presence of a normal pylorus, may be an acquired lesion.

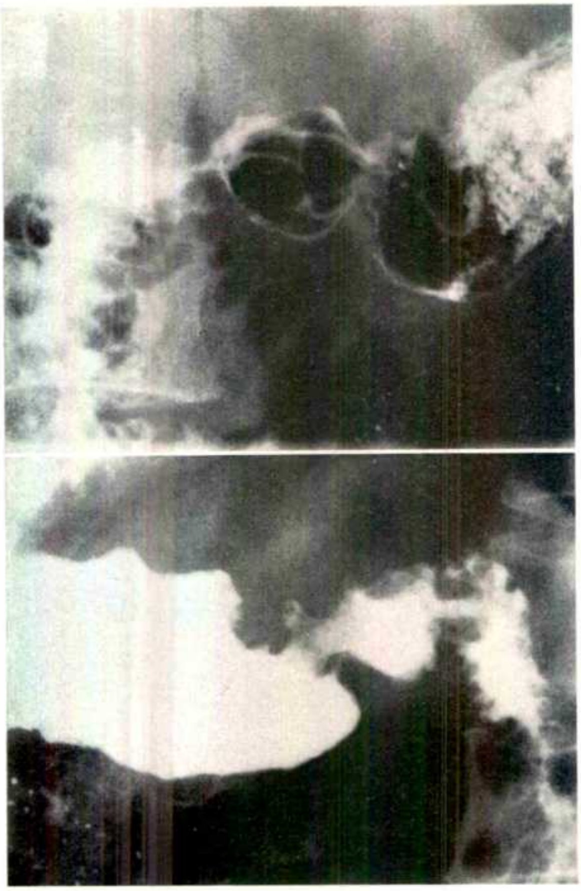


FIG. 1.

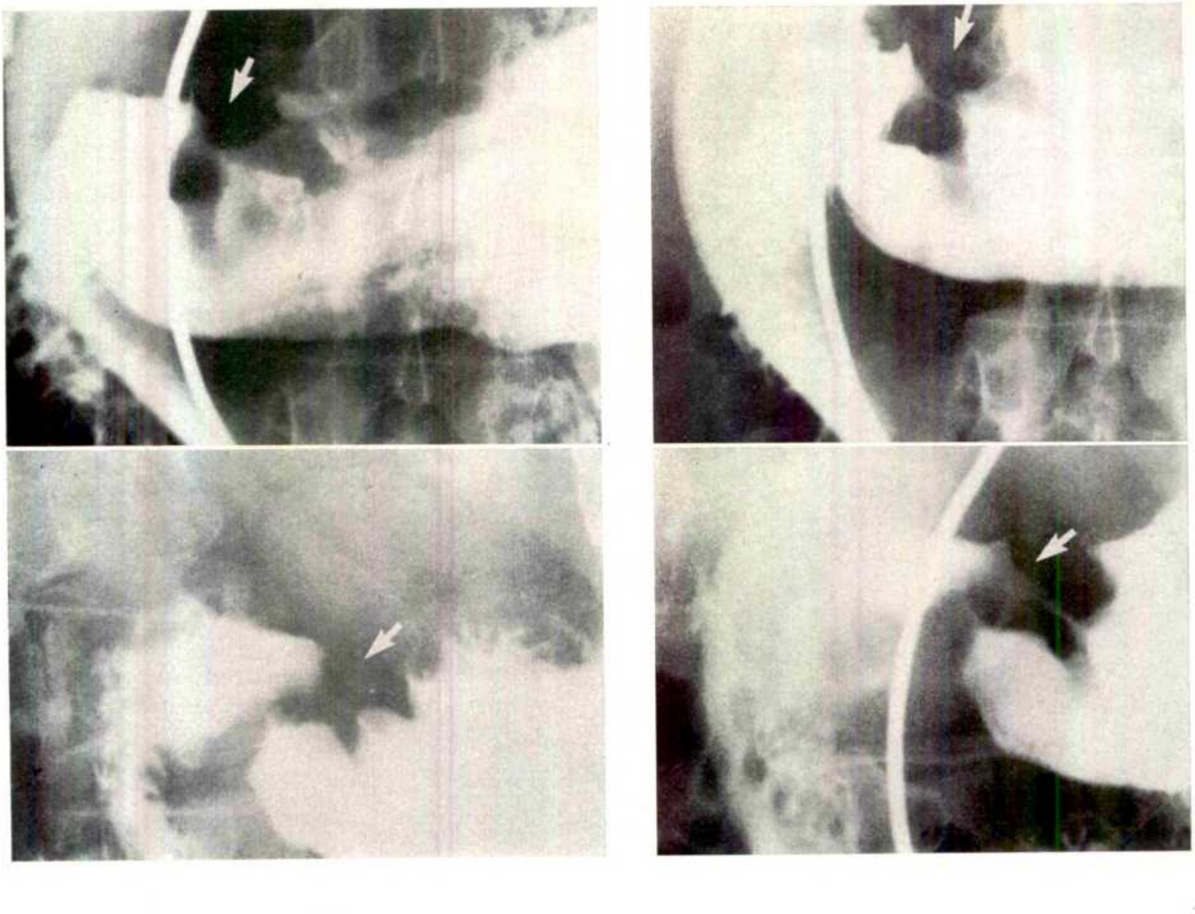
Ulcer in the prepyloric region. The films show no change in size or position of the ulcer when compared with films taken eight months previously.

One of the cases reported by Farack *et al.* (1974) illustrates a similar mode of development of gastro-duodenal fistula from a previous ulcer. However, this is the first reported case where clinical relief of symptoms was related to the establishment of the fistula. One may suggest that formation of this second channel may reduce the patients pains by improving emptying of the stomach.

Gastric retention was never found in this particular patient. Nevertheless, taking his clinical improvement into consideration, the function of his spontaneous fistula might be compared with those made by operative gastro-duodenostomies (Lechner, Riedl and Dinstl, 1973).

FIG. 2. (*Below*)

Two months later at the site of the previous ulcer, distortion of the gastric wall can be seen; most likely because of post-ulcerative shrinkage and traction on the gastric wall. A narrow fistula is demonstrated between the previous ulcer site and the duodenum, with patient in different positions (arrow).



1976, *British Journal of Radiology*, *49*, 92–94

REFERENCES

Christien, G., Branthamme, J. M., Volny, L., Deschamps, P., and Morice, A., 1971. Pylore double: malformation congénitale. *Semaine des hôspitaux de Paris*, *40*, 1485–1488.

Drapkin, R. L., Otsuka, A. L., Castellanos, H. L., El Hindi, S., Nowicka, H., and Levitan, R., 1974. Acquisition of a pyloric septum or pyloric duodenal fistula. *Gastroenterology*, *66*, 1234–1236.

Farack, U. M., Goresky, C. A., Jabbari, M., and Kinnear, D. G., 1974. Double pylorus: A hypothesis concerning its pathogenesis. *Gastroenterology*, *66*, 596–600.

Hansen, O. H., Kronborg, O., and Pedersen, T., 1972. The double pylorus. *Scandinavian Journal of Gastroenterology*, 7, 695–696.

Lechner, G., Riedl, P., and Dinstl, K., 1973. Röntgenmorphologische und funktionelle Veränderungen am Magenausgang nach Vagotomie und Drainageoperationen. Bruns' *Beiträge zur klinischer Chirurgie*, *220*, 405–412.

A venous malformation of the cavernous sinus

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(*Received April, 1975*)

The clinical features and radiological demonstration of a previously unreported venous malformation of the cavernous sinus are described.

Case history

A 13-year-old boy was first seen by an ophthalmologist at one year of age when his mother noticed unequal pupils. At four years of age, his right eye started to protrude and a diagnosis of a cyst behind the right eye was made by a neurologist and ophthalmologist.

At four and a half years, the child was referred to an orthoptist and his findings were as follows:—

Paresis of the right superior oblique and inferior oblique muscles and overaction of the left superior and inferior oblique muscles. Intermittent left hypertropia or right hypotropia for near distance. Right ptosis when tired. The right pupil was slightly larger than the left.

Previous Medical History

The child was born by Caesarian section. He has recurrent tonsilitis. There is no history of trauma or fits. There is no relevant family history.

Recent Clinical Findings

(November 13, 1971)

An otherwise healthy, white, 13-year-old male presenting with slight proptosis of the right eye. Exophthalmometer readings—right eye, 15 mm; left eye, 13 mm. No bruit was heard and no abnormality of conjunctival veins was observed. There was drooping of the right lid but it was difficult to determine whether this was due to levator weakness or to habit closure of the lid in order to suppress the image coming from this eye.

Movements of the Eye

In the primary position of gaze, fixation was done by the left eye and the right eye was observed in a downward and inward position. There was no movement of the right eye past the midline. Left hyperphoria was seen in laevoversion and elevation. Diplopia was not elicited in any position of gaze.

The corneal sensation and skin temperature of the face were normal and there was no anhydria. The maxillary and mandibular nerves were normal. The left pupil was larger than the right. However, direct and consensual light reflexes were brisk. Media, fundi, tensions and fields were all normal. Corrected visual acuity both sides = 6/5.

A clinical diagnosis was made of a partial right oculomotor nerve and right abducens nerve lesion associated with slight proptosis. Sympathetic involvement was postulated to explain the constricted right pupil.

A lesion situated in the anterior aspect of the right cavernous sinus was diagnosed and the patient was sent for radiological investigation.

Radiological Findings

A plain occipito-frontal view of the orbits (Fig. 1) showed the presence of opacities, varying in size from 1 to 2 mm, superimposed on the right sphenoidal fissure and its margins. The margins of the fissure as well as the greater wing of the sphenoid showed diminution of bone density compared with the normal left side.

The opacities were not visible on the plain lateral view, but were clearly demonstrable on both antero-posterior and lateral polytomography (Figs. 2 and 3) to be lying within the anterior portion of the cavernous sinus. The medial wall of the cavernous sinus was seen to be intact and the pituitary fossa was normal.

Right common carotid angiography demonstrated normal internal and external carotid arteries. No "tumour" vessels were seen in the right orbit or in the right cavernous sinus.

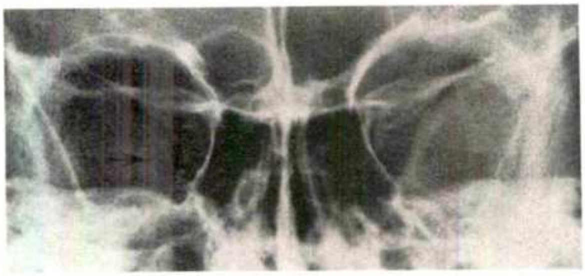

FIG. 1.
Opacities overlying the right sphenoidal fissure (black arrow).

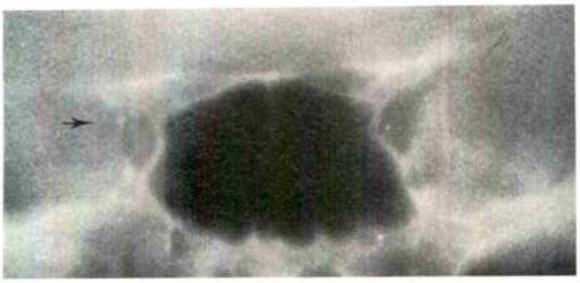

FIG. 2.
Antero-posterior tomography demonstrating the position of the opacities (black arrow) at the level of the anterior clinoid process.

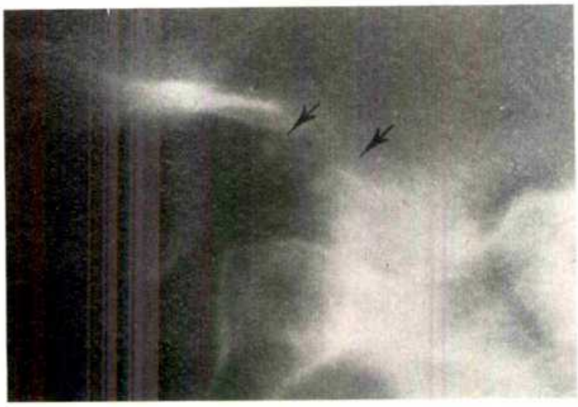

Fig. 3.
Lateral tomography demonstrating the position of the opacities below and behind the anterior clinoid process (black arrows).

Orbital venography (Figs. 4 and 5) was carried out via a vein in the right frontal region. No abnormality was seen in the orbital veins. There was a large inferior orbital vein on the left side, but this is probably within normal limits. A collection of small "haphazard" veins was seen in the anterior portion of the right cavernous sinus corresponding exactly with the opacities seen in the plain films and on polytomography.

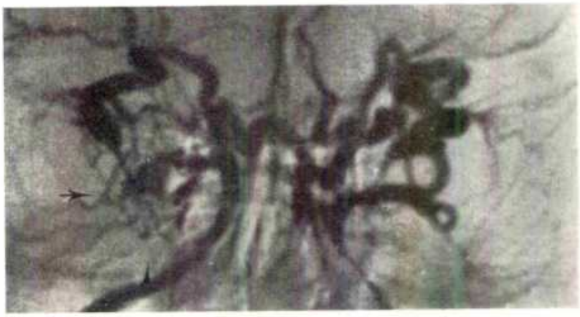

FIG. 4.
Postero-anterior subtraction view of orbital venogram showing "abnormal" vessels (black arrows) overlying the right orbit.

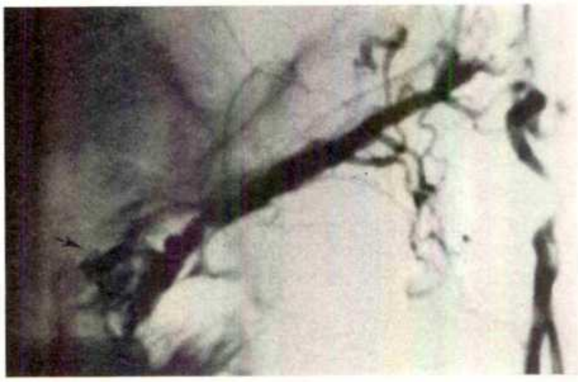

FIG. 5.
Lateral subtraction view of orbital venogram showing the position of the abnormal vessels in the cavernous sinus.

DISCUSSION

The radiological appearances in this patient suggest a vascular malformation in the anterior portion of the right cavernous sinus.

The fact that it opacifies on orbital venography and not on arteriography, together with the opacities which are thought to be phleboliths, would suggest that the lesion is a venous malformation.

The shape of the cavernous sinus varies considerably. According to Viallefont, Paleirac and Boudet (1959), there are three fundamental types:

(1) A single large venous trunk on either side of the sella tursica.

(2) A sinus composed of several individual veins running in a general antero-posterior direction.

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(3) A plexiform type where the sinus is composed of a multitude of small veins with rich anastomoses. The lumen of the sinus is traversed by trabeculae giving it the appearance of spongy tissue.

Although the right cavernous sinus in this patient appears to consist of multiple channels, the calcification demonstrated within it must be considered as being pathological. Haemangiomata and varices in the orbit are well described (Viallemonte *et al.*, 1959).

In some patients a venous malformation may extend outside the orbit into the middle fossa (Hanafee, Sing and Dayton, 1968), through an enlarged sphenoidal fissure (Brauston and Norton, 1963), onto the scalp, frontal bone or hard palate (Lloyd, Wright and Norman, 1971). Lloyd (1974) also describes two patients in whom a haemangioma within the muscle cone was associated with abnormal veins remote from the site of the haemangioma. In both patients these veins lay on the lateral orbital wall.

The patient being described showed no evidence of a venous abnormality within the orbit and there was no evidence of an anomaly elsewhere in the skull or face. The condition at the present time is stable and surgery is not contemplated in the immediate future.

CONCLUSIONS

A hitherto undescribed entity of a venous malformation of the right cavernous sinus is described in a 14-year-old boy with proptosis and evidence of involvement of the right sympathetic and third and sixth cranial nerves. The lesion is confined to the cavernous sinus and there is no evidence of a concomitant intra- or extra-orbital venous malformation or of an intra-cranial arterio-venous anomaly.

ACKNOWLEDGMENT

We are indebted to Dr. G. Lloyd for his valuable opinion on the radiological changes in this case.

REFERENCES

BRAUSTON, B. B., and NORTON, E. N. D., 1963. Intermittent exophthalmos. *American Journal of Ophthalmology*, *55*, 701–708.

HANAFEE, W. N., SING, P. C., and DAYTON, G. O., 1968. Orbital venography. *American Journal of Roentgenology*, *104*, 29–35.

LLOYD, G. A. S., WRIGHT, J. E., and MORGAN, G., 1971. Venous malformation in the orbit. *British Journal of Ophthalmology*, *55*, 505–516.

LLOYD, G. A. S., 1974. Pathological veins in the orbit. *British Journal of Radiology*, *47*, 570–578.

VIALLEFONT, H., PALEIRAC, R., and BOUDET, C., 1959. The radiological examination of the cavernous sinuses. *Bulletin de la Société Franc Opthalmology 72*, 200–219.

Renal cortical necrosis and papillary necrosis in an infant

By M. R. Funston, M.B.B.Ch., D.M.R.D., B. J. Cremin, F.R.A.C.R., F.R.C.R., and I. J. K. Tidbury M.B.Ch.B.

Department of Radiology, Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa

(*Submitted March, 1975 and in revised form May, 1975*)

Bilateral renal cortical necrosis (BRCN) and renal papillary necrosis have been reported in infancy as a complication of gastro-enteritis, perinatal asphyxia, utero-placental haemorrhage, septicaemia, exsanguination, kernicterus, eclampsia, renal vein thrombosis, fetomaternal transfusion and anoxic shock (Mauer and Nogrady, 1969; Leonidas, Berdon and Gribetz, 1971). We wish to report a case of combined BRCN and papillary necrosis, with some unusual radiological findings.

Case history

A female infant aged three months presented with a four-day history of severe gastro-enteritis followed by convulsions. She was oliguric with metabolic acidosis. The urine contained protein and red cells. The blood urea was 184 and the serum creatinine 2·5 mg/100 ml. The patient had a spontaneous diuresis without requiring dialysis. In the diuretic phase fluid, electrolyte and acid-base balance was corrected with difficulty.

Four weeks after the onset of the illness, an excretory urogram was performed. At the time of the examination the infant was well hydrated, polyuric, and 20 ml. of sodium iothalamate 54 per cent W/V (Conray 325) was injected intravenously. No calcification was present on the control film of the abdomen. Both kidneys were enlarged, measuring 7·5 cm in length. Prompt opacification of the calyces was seen, and all the calyces were noted to be dilated. The ureters were of normal calibre and there was no ureteric or bladder outlet obstruction. A striking feature was dense opacification of the renal cortex and the columns of Bertin, which occurred five minutes after injection of the contrast. The medullary zones were distinctly less opacified. This difference in opacification of the cortex and medulla persisted for 30 minutes. After one hour there was a steady increase in overall kidney density, with equal opacification of the cortex and medulla, which persisted for four days (Fig. 1).

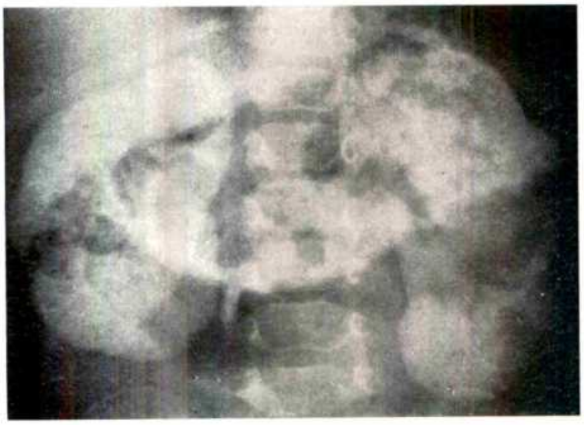

FIG. 1.
Excretory urogram (four-day film) showing enlargement of the kidneys and a prolonged dense nephrogram.

At the time of this excretory urogram the patient was in the diuretic phase of acute renal failure with a blood urea of 205 mg/100 ml., and there was no reduction in urine output during or after urography. A retrograde uretero-pyelogram showed that the ureters were of normal calibre but bilateral caliectasis was again demonstrated. The absence of ureteric or bladder outlet obstruction was confirmed.

Nine weeks after the onset of the illness, bilateral "tram-line" cortical calcification, with calcification of the columns of Bertin, was observed on a plain radiograph of the abdomen (Fig. 2). This calcification was only demonstrated with the patient prone and using a low kilovoltage technique. The calcification had completely disappeared 12 weeks later, and a repeat excretory urogram at this stage revealed the typical calyceal changes of papillary necrosis. There was a marked reduction in renal size when compared with the initial urogram. At this time the patient's renal function had returned to normal.

DISCUSSION

There are numerous reports in the literature of bilateral renal cortical necrosis in infancy (Leonidas *et al.*, 1971; Eskeland and Skogrand, 1959; Mauer and Nogrady, 1969), but the radiographic finding of cortical calcification following this disease in infancy has rarely been observed. Leonidas *et al.* (1971) and Whelan, Ling and Davis (1967) reported cases of bilateral renal cortical necrosis in infancy followed by cortical calcification. The cortical calcification observed in our patient was not visible on a radiograph exposed with the usual radiographic factors employed for a plain film of the abdomen in an infant. It was only demonstrated using a low kilovoltage technique, with the patient in the prone position, and was not observed in the radiograph taken three months later. We speculate, therefore, that there may be two reasons why this calcification is not more frequently reported in infancy: optimum radiographic factors are not employed, and the calcification may often be temporary.

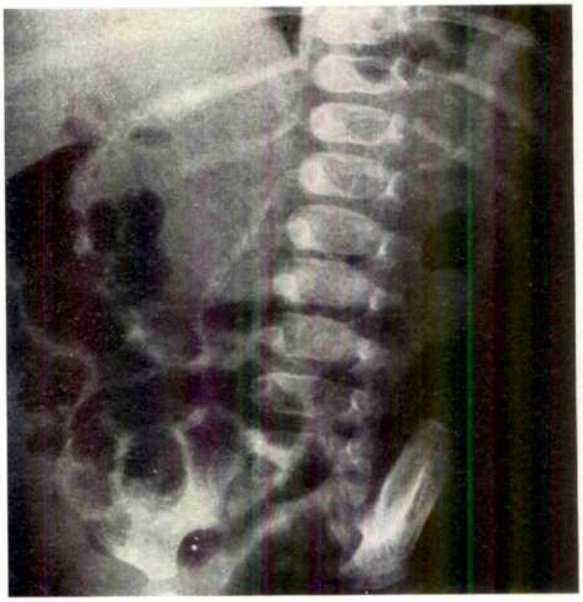

FIG. 2.
LogEtronic print of a radiograph of the upper abdomen showing cortical calcification of the right kidney.

The dilatation of the calyces without evidence of obstruction observed in the initial urogram in our patient was considered to be due to swelling of the papillae as a result of papillary necrosis. Changes observed in the subsequent urogram were typical of papillary necrosis, with evidence of sloughed papillae and a reduction in size.

Chrispin *et al.* (1970) and Chrispin (1972) reported heavy opacification by contrast medium of the medullary zones in medullary necrosis. A uniformly dense nephrogram soon after the injection of contrast medium has been reported in patients with acute tubular necrosis by Fry and Cattell (1972). This phenomenon is thought to be the result of leakage of contrast medium into the interstitial space of the kidney. In our patient, however, the heavy opacification occurred in the cortex and the septal columns of Bertin, while the medullary zones appeared relatively radio-translucent. This appearance has not been previously reported. One can only postulate that the degree of tubular damage in the cortex was greater than in the medulla, allowing a greater amount of leakage to occur into the interstitial space of the cortex.

The prolonged dense nephrogram, despite prompt calyceal filling, observed in our patient is thought to be the result of the same process, *viz.* leakage into the interstitial space. Berdon *et al.* (1969) have reported similar findings. These authors speculated

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that Tamm-Horsfall protein has been precipitated by contrast medium, resulting in tubular blockage and producing a uniformly prolonged tubular nephrogram. However, all their patients were oliguric at the time of excretory urography, whereas our patient was well-hydrated and polyuric. It is therefore unlikely that protein-precipitation was the cause for the prolonged nephrogram in our patient.

ACKNOWLEDGMENTS

This case was examined during a visit of Dr. W. Berdon of Columbia University and Dr. G. Friedland of the Bowman Grey School of Medicine. They were both most helpful in corroborating our diagnosis, and we are grateful to Dr. Friedland for his suggestion of taking the prone low kilo-voltage film, and his help in acquiring the LogEtronic reproduction of Fig. 2.

REFERENCES

BERDON, W. E., SCHWARTZ, R. H., BECKER, J., and BAKER, D. H., 1969. Tamm-Horsfall proteinuria. Its relationship to prolonged nephrogram in infants and children and to renal failure following intravenous urography in adults with multiple myeloma. *Radiology*, *92*, 714–722.

CHRISPIN, A. R., 1972. Medullary necrosis in infancy. *British Medical Bulletin*, *28*, 233–236.

CHRISPIN, A. R., HULL, D., LILLIE, J. G., and RIDSON, R. A., 1970. Renal tubular necrosis and papillary necrosis after gastro-enteritis in infants. *British Medical Journal*, *1*, 410–412.

ESKELAND, G., and SKOGRAND, A., 1959. Bilateral cortical necrosis of the kidneys in infancy. *Acta Paediatrica*, *48*, 278–286.

FRY, I. K., and CATTELL, W. R., 1972. The nephrographic pattern during excretion urography. *British Medical Bulletin*, *28*, 227–232.

LEONIDAS, J. C., BERDON, W. E., and GRIBETZ, D., 1971. Bilateral renal cortical necrosis in the newborn infant: Roentgenographic diagnosis. *The Journal of Paediatrics*, *79*, 623–627.

MCALLISTER, W. H., and NEDELMAN, S. H., 1961. The Roentgen manifestations of bilateral renal cortical necrosis. *American Journal of Roentgenology*, *86*, 129.

MAUER, S. M., and NOGRADY, M. B., 1969. Renal papillary and cortical necrosis in a newborn infant: Report of a survivor with roentgenolic documentation. *The Journal of Paediatrics*, *74*, 750–754.

WHELAN, J. G., LING, J. T., and DAVIS, L. A., 1967. Antemortem Roentgen manifestations of bilateral renal cortical necrosis. *Radiology*, *89*, 682–689.

Book reviews

Radionuclide Scanning in Cyanotic Heart Disease. By Gary F. Gates, M.D., pp. xi + 100, 1974. (Charles C. Thomas, Illinois, USA), $15.00.

The earnest reader who sees the title of this book might be misled into thinking that he was about to possess a monograph covering a subject: the use of radionuclides as a non-invasive way of investigating cyanotic congenital heart disease. He would be disappointed. The book is not a review, but is a paper describing one technique (and not a very good technique).

What is described depends on the fact that if radioactive particles are injected intravenously, they normally lodge in the lung; those that end up elsewhere represent a right to left shunt the size of which can be calculated from the relative number of particles. The method described assembles a series of pictures using a gamma-camera from which the data are calculated. I found it difficult to understand how allowance is made for overlaps of pictures and no mention is made of scatter from one view to another or varying soft-tissue attenuation. However, correlations with results obtained at catheterization are good, and undoubtedly shunts can be assessed by the methods described. The implication of the text suggests that catheterization and angiography can be avoided, but manifestly this is not so. I think if this fairly simple technique were presented as a baseline observation and for follow-up after surgery, then the work would be more realistic. It still does not seem to me to deserve being turned into a monograph.

J. P. LAVENDER

The Accessory Digestive Organs. Edited by R. E. Wise and A. P. O'Keeffe, pp. xi + 331 (illus), 1975 (Year Book Medical Publishers), £15·40.

This book, part of the series sponsored by the American College of Radiologists, is divided into five parts:

(1) the pancreas;
(2) the liver;
(3) the extra-hepatic bile-ducts;
(4) the gall-bladder;
(5) the salivary glands.

Each section consists of a number of case reports, with accompanying radiographs, preceded by a short description of the pathology found at that site. The radiographs are of superb quality, and illustrate clearly the varying points which one must consider in reaching a correct diagnosis.

The author's use of the term "proper hepatic artery" is, however, both old-fashioned and likely to lead to confusion. The references are practically all from the American literature, and one might finally question the need, other than for illustrative purposes, of invasive investigation of such overt pathology.

The book is expensive and will be of use only to a very limited audience.

J. A. GLEESON.

1976, *British Journal of Radiology*, *49*, 97–98

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

MIXED SCLEROSING BONE DYSTROPHY WITH REGRESSION OF MELORHEOSTOSIS

I read with interest the case report by J. A. Kanis and J. G. Thomson (*British Journal of Radiology*, *48*, 400). Their patient shows unilateral involvement of the long bones by endosteal sclerosis and osteopoikilosis in the right knee. In view of the rarity of these bone dysplasias it seems of interest to refer to a case of melorheostosis with involvement of all extremities, the pelvis and the sacrum (Elkeles, 1956). It was the third case in the medical literature showing this unusually widespread involvement of the skeletal system.

The patient was a male, 24 years of age, with a deformity of his left knee which had been present since birth. The left leg was shortened by 2 in. There was also bilateral inner-ear deafness.

Radiologically, the widespread bony lesions consistent with melorheostosis were complicated by the presence of osteopoikilosis, osteopathia striatum and the monostotic type of polyostotic fibrosis dysplasia in individual bones.

The increasing number of case reports in recent years showing the co-existence of two or more of these bone dysplasias suggests that they belong to the same group of congenital bone diseases. It seems likely that they are the result of a defect in the mesenchymal tissue which manifests itself in the form of more or less widespread, sclerotic, fibrotic or fibro-cystic changes. Either of these abnormal structures may develop as the dominant feature in ensuing disease.

Yours, etc.,
A. ELKELES.

X-ray Department,
Prince of Wales's General Hospital,
London, N.15.

REFERENCE

ELKELES, A., 1956. Melorheostosis, report of a case affecting all extremities. *Indian Journal of Radiology*, souvenir number, 1–7.

THE EDITOR—SIR,

WALL VACUUM SUCTION FOR EVACUATING PLASTIC VACUUM CASSETTES OF "LO DOSE" TYPE FOR MAMMOGRAPHY

The possible use of hospital piped suction in evacuating vacuum cassettes for mammography is not widely known and may be of great help to a number of readers.

Two types of vacuum cassettes are available:

(1) A semi-disposable type which needs heat sealing; and
(2) a stronger version, fitted with a car-tyre type of valve and a clip to help hold together the suction self-sealing open end. (The E-Z-EM'S Vac-u-Pak bag.)

Type 1 needs an expensive vacuum pack apparatus, but Type 2 can be supplied with a small hand pump.

It seems to us that the plastic tube leading to the adaptor into which the car-type valve fits, might readily fit on to a hospital standard wall suction outlet (*i.e.* directly on to its tap outlet, after disconnecting the bottle system). This indeed proved true, and since the main vacuum suction line in our hospital passes along the outside wall of the radiographic room where mammography is carried out, we were readily able to arrange a spur through the wall to a standard suction-tap outlet.

The cassettes are thus loaded in the dark-room and evacuated in the radiographic room. Incidentally the apparatus may also be used as a sucker! Since it would seem likely that many other radiology departments are likely to have easy access to such a suction line they may wish to consider using it in this way.

Yours, etc.,
F. W. WRIGHT.

X-ray Department,
The Churchill Hospital,
Headington,
Oxford OX3 7LJ.

THE EDITOR,—SIR

MUST RADIOLOGISTS DO ALL THE REPORTING?

Dr. R. M. Emrys-Roberts can be assured that radiologists may hardly be accused of excessive litigophobia, but one certainly cannot reassure him that semi-trained substitutes for radiologists would not very speedily become litigophobic when they discovered that they had to commit their reports and opinions to *paper*.

The question is not simply whether the radiologists (tempted though they may be, in face of oppressive workloads) will "allow" them to do so, but whether they can ever be *appointed* to do so. Presumably this would eventually be decided by the senior administration of the N.H.S., prompted by suitable radiological and legal advice.

It seems likely that this decision would indicate that official, final X-ray reports should not be given by "substitutes". In reality there can only be yawning gaps in the provision of proper X-ray services and lowering of standards, until there are more fully-trained radiologists available.

Yours, etc.,
A. R. MANNERS.

Consultant Radiologist,
North Tees General Hospital,
Hardwick, Stockton-on-Tees,
Cleveland TS19 8PE.

THE EDITOR—SIR,

MUST RADIOLOGISTS DO ALL THE REPORTING?

No one can claim a monopoly of knowledge, particularly in medicine, but the profession has rightly evolved a system of training and examinations for those who wish to narrow their field to particular skills and areas. The patient has a right to expect that where such a person is available his expertise should be exercised on their behalf. Thus, where a radiologist is available, he should report on all radiographs, as well as undertaking the more specialized radiological procedures. Where radiologists are not available, the patients are getting less than they have a right to expect if their radiographs are not so reported upon, and they become in this respect second-class citizens.

The answer lies in training sufficient radiologists and improving their working conditions, so that the community hospitals have full radiological cover and their patients the first-class service they are entitled to expect.

Yours, etc.,
G. EVISON.

Westfield Lodge,
Weston Road,
Bath.

THE EDITOR—SIR,

MUST RADIOLOGISTS DO ALL THE REPORTING?

With the ever-increasing work-load in X-ray departments, there would seem to be three main areas which could usefully bear examination with a view to increasing both efficiency within the department and acceptance outside of the importance of radiology in diagnosis—orthopaedics, casualty and community care.

By agreement with our orthopaedic colleagues, for example, we have for the past three years not reported on fracture follow-up films unless an opinion is specifically requested. This policy has significantly improved working relations between the X-ray and orthopaedic departments—no longer do we insist on films being sent to the X-ray department from the orthopaedic wards to issue reports which are neither needed nor read! Instead, regular combined orthopaedic clinico-radiological meetings within the X-ray department have developed and are proving invaluable.

As far as casualty is concerned, in its 1974–5 annual report, the Royal College states that these radiographs should be given high priority by radiologists. This would in no way appear to encourage a more rational and clinical approach to diagnostic radiology. Is it not more realistic to give casualty reporting the *lowest* priority until such time that the service ceases to be loaded by "medico-legal" trivia? In my experience, where a report is essential, an opinion is invariably requested. By removing this "prop" we may play our part in improving the quality of the casualty department itself. More important, we may create a steady pressure to help reduce the widespread abuse of casualty and X-ray services.

Community care also has its particular problems, and while sympathetic to the points raised by Dr. R. M. Emrys-Roberts, I should like to express my firm support for the current policy of the Royal College of Radiologists on insisting that the right place for modern X-ray departments is within the larger unit on economic and clinical grounds. By all means, let us encourage the general practitioner to see his films, but within the district hospital where a radiologist is available for consultation.

In conclusion, the principle of delegating routine work to technicians (Thompson, 1974) or clinical assistants may be a good one providing training is adequate. However, the present acute shortage as far as radiology is concerned can only be corrected in the long term by more radiology instruction to undergraduates, *by radiologists*, which would encourage more graduates to enter this speciality and may also lead to a more intelligent use of X-ray departments in general.

Yours, etc.,
B. M. GOMPELS.

Radiology Department,
Epsom District Hospital,
Epsom, Surrey.

REFERENCES

THOMPSON, T. T., 1974. The evaluation of physician's assistants in radiology. *Radiology*, *111*, 603–606.

Annual Report of Council, 1974–75. The Royal College of Radiologists.

Forthcoming events and other notices

The editors have decided that owing to the extreme shortage of space in the *British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and meetings announcements specifically connected with the British Institute of Radiology and its associated bodies. Members, however, will be receiving future meetings announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

The following meetings are to be held at Institute House, 32 Welbeck Street, London W1M 7PG.

Measurements of Radiobiological Parameters in Humans, January 16, 1976

Whole-Body Scanning, January 16, 1976

The Use of Hyperthermia and Non-Ionizing Radiation in the Treatment of Cancer, May 21, 1976

Further information from the General Secretary.

Radionuclides in Tumour Localization and Staging

An all-day meeting organized by the Nuclear Medicine Committee of the British Institute of Radiology is to be held at the Middlesex Hospital, London, W.1, on Wednesday, February 18, 1976.

Further information from the General Secretary, at 32 Welbeck Street, London, W 1.

Second-Stage Carcinoma of the Cervix

A meeting organized jointly by the Royal Society of Medicine, Section of Radiology, The British Institute of Radiology and the Royal College of Radiologists to be held February 20, 1976.

For further information please contact Royal Society of Medicine, 1 Wimpole Street, London, W.1.

Annual Congress and Scientific Exhibition

To be held on April 8–9, 1976 at the University College, London. For information and registration please contact the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiology of Visceral Venous Obstruction

The Mackenzie Davidson Memorial Lecture, by Dr. M. Viamonte, Director of Radiology, University of Miami, School of Medicine, to be given at the University College, London, April 8, 1976.

Medical Images: Formation, Perception and Measurement

The Seventh L. H. Gray Conference, which will be concerned with the fundamentals of medical images, will be held at the University of Leeds, England, on April 13–15, 1976. The purpose of the conference is to concentrate attention on the unifying principles which underline the variety of imaging techniques now used in medicine. It is hoped to maintain the international character of the previous conferences.

Two half-day sessions will be concerned with the performance of new imaging devices of diverse types and with general methods for assessment of instrument performance. These will be followed by two sessions on physical and visual aspects of the detection and perception of image information. The fifth session will deal with the extraction of numerical information from images, and will be followed by a review of the overall conference theme. It is expected that speakers will illustrate their topics by specific examples from fields such as medical radiology, cytology, nuclear medicine, ultrasonics, computer-processing, etc.

In order to achieve a coherent scientific programme, speakers are being arranged chiefly by invitation. However, it is hoped that papers will provoke substantial contributions from participants in the discussions, and that these will be published in the conference proceedings.

There will be an exhibition of imaging devices.

Address for further information: Dr. M. J. Day, Regional Medical Physics Department, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, England.

Postgraduate Course in Tomography of the Temporal Bone

To be held in Copenhagen, June 3–4, 1976. The course is sponsored by the I.C.R., the A.E.R. and the Scandinavian Association of Radiologists, and will be directed by Dr. Sam Brünner, president of the Congress.

Experts in the various fields will lecture on the techniques, diagnostic findings interpretations, advantages and limitations of the different procedures. The fee for the course is $150, and includes lunches, dinner and the syllabus.

For further information and registration, please contact Dr. Paul E. Andersen, Department of Radiology, University Hospital, 5000 Odense, Denmark.

Computers in Radiotherapy in Europe

It is proposed to hold a Workshop at IAEA, Vienna on July 5–10, 1976, organized by the Groupe Informatique, A.E.R. with the support of the European Association of Radiology. The aim will be to establish the contribution that the computer makes at the clinical level in the fields of dose computation, clinical records, radiobiology, etc., and to determine future development.

Further information from Dr. D. N. Edwards, Clinical Research Unit, Mersey Regional Centre for Radiotherapy and Oncology, Clatterbridge Hospital, Bebington, Wirrall, Merseyside L63 4JY, U.K.; or Dr. T. Moller, Radioterapikliniken, Lasarettet, S-221 85 Lund, Sweden.

XIV International Congress of Radiology

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colégio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Obituary

Professor Gordon Hamilton Fairley, M.A., B.M.B.Ch., M.R.C.P., D.M.

Apart from being an outstandingly able physician, Gordon Hamilton Fairley was also a very warm one. He cherished life, and was dedicated to preserving it. Thus, his death on October 23, 1975 was especially sad and tragic. While peacefully walking his dog in the heart of London he was wantonly destroyed by a bomb.

As Professor of Medical Oncology at St. Bartholomew's Hospital in the chair founded by the Imperial Cancer Research Fund, Gordon Hamilton Fairley had contributed a very great deal to the chemotherapy and immunology of malignant disease and, in particular, the treatment of the malignant reticuloses.

A man of great energy and enthusiasm, he always managed to bring out the best in his colleagues. His intellectual honesty made him a first-class research worker. His gaiety and personal charm inspired all those around him, patients and colleagues alike, to greater effort. The incorporation of various disciplines, both diagnostic and therapeutic, into a coherent unit was one of Gordon's pioneering visions and successes. He was, himself, an excellent diagnostic radiologist, especially on chest disease.

He had the human touch, with a deep regard for his patients. Their social circumstances, occupations and needs were always taken into account when planning investigation and treatment.

As a teacher and lecturer he was popular the world over, yet during his travels he always managed to steal a few minutes to visit the museums and art galleries. He shared the trait of other truly busy men, of wide-ranging interests, from a love of Impressionist paintings to dinghy sailing.

While extending our deepest sympathy to his wife and children in their tragic bereavement, we remain stunned by his loss.

A.K.T.

Instructions to authors

Please keep manuscripts brief and concise and include only those illustrations essential to an understanding of the text.

Much time and correspondence will be saved if authors pay careful attention to these detailed instructions.

Material published in THE BRITISH JOURNAL OF RADIOLOGY includes full papers, case reports, technical and instrumental notes, letters to the editor and invited articles. Communications should ordinarily be addressed to the Honorary Editors, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Communications from North America or Australasia should preferably be submitted to the most appropriate of the following Associate Editors:

Dr. G. P. G. Sim, X-ray Department, Wellington Hospital, Wellington, New Zealand.

Dr. H. A. Luke, The Alfred Hospital, Prahran, 3181, Victoria, Australia.

R. W. Stanford, Esq., M.A., Department of Medical Physics, Royal Perth Hospital, Perth, Western Australia.

Dr. J. R. Cunningham, Physics Division, The Ontario Cancer Institute, 500 Sherbourne Street, Toronto 5, Canada.

The acceptance of a paper for publication in THE BRITISH JOURNAL OF RADIOLOGY is at the discretion of the Editors and is subject to the understanding that the material contained in the paper has not already been published and is not intended for publication elsewhere.

The Editors take no responsibility for the return of MSS, prints, etc. submitted for publication.

MANUSCRIPT. The manuscript should be typewritten in English on one side of the paper only with double spacing and margins of at least 25 mm (1 in.) on both sides and at the top. The top copy must be submitted together with one duplicate. The address given in the title should be that of the department(s) or hospital(s) at which the work was carried out. If any author has subsequently moved to a new address, this should be given as a footnote. Degrees and diplomas of authors should be given. Tables (numbered I, II, etc.) should be given on separate sheets, and each should have a short descriptive title. Legends for illustrations, including diagrams and graphs, should be set out on a separate sheet, and denoted Fig. 1, 2, etc. The initial letter of trade or proprietary names should be a capital. Mathematical expressions should be set out very clearly, using printed letters rather than script, especially where suffixes and indices are involved.

UNITS, SYMBOLS AND ABBREVIATIONS

Authors are encouraged to adopt the *International System of Units* (*SI*),[1;2] combined with the special units recommended by the International Commission on Radiation Units and Measurements (ICRU).[2] Further details are given in *Changing to the Metric System.*[3] The publication *Units, Symbols and Abbreviations: a Guide for Biological and Medical Editors and Authors*[4] is thoughtful and critical on this subject; authors are strongly recommended to follow the detailed suggestions in this Guide and to note particularly the comments made on the choice of units.

DIAGRAMS AND GRAPHS. Diagrams and graphs, including numerals and lettering, should be clearly drawn in indian ink on white card or blue tracing paper. The size should not exceed 355 × 304 mm (14 × 12 in.). In general they will be reduced to have a horizontal dimension of 76 mm (3 in.) and their scale, thickness of line and lettering should allow for this reduction. Photographic prints of diagrams can also be accepted. The reproduction of graph paper requires the making of half-tone blocks and will normally not be acceptable. The figure number, author's name and title of article should be pencilled lightly on the back of each illustration.

Authors of physics papers will find advice on drawing diagrams, particularly electrical circuits, in *Notes for Authors*[5] issued by the Institute of Physics and the Physical Society.

RADIOGRAPHS. Unmounted prints not larger than whole plate, 216 × 152 mm ($8\frac{1}{2} \times 6\frac{1}{2}$ in.), and not smaller than half plate should be supplied with MSS; if the prints are not of sufficiently high standard for reproduction purposes the author will be required to submit the original radiographs and to defray the cost of making prints. Tracings of sections of prints are acceptable when necessary for additional clarification. Hospital illustrators and photographers are usually familiar with the style of drawing or print which will give the best reproduction.

COLOUR. Drawings or photographs in colour are very expensive and are acceptable only if the author is prepared to pay the additional cost of *block-making and printing*.

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[1] *The International System of Units* (*SI*). British Standard 3763, 1970. British Standards Institution, London (£2·70).

[2] *A guide to International Recommendations on Names and Symbols for Quantities and on Units of Measurement.* W.H.O. (Sw. fr. 48).

[3] *Radiation Quantities and Units ICRU Report 11*, 1968. ICRU, 4201, Connecticut Avenue, N.W., Washington D.C.20008, U.S.A.

[4] *Changing to the Metric System*, 4th ed., 1969. H.M.S.O., London (40p).

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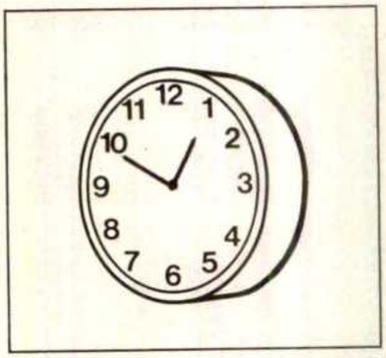

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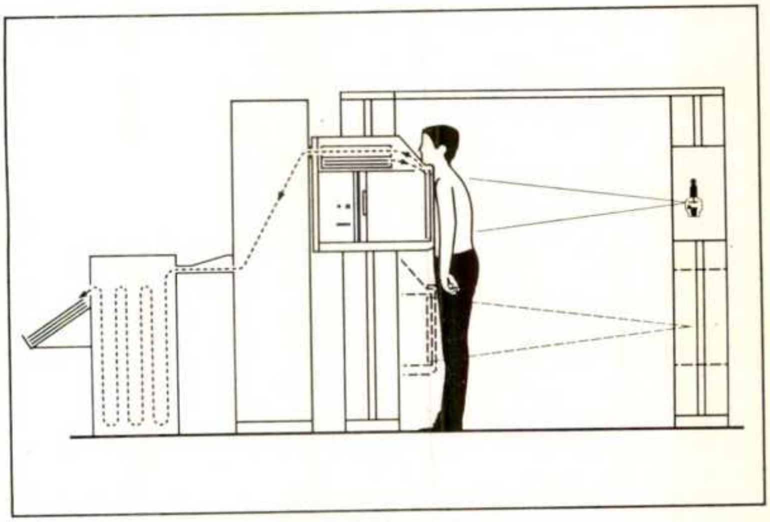

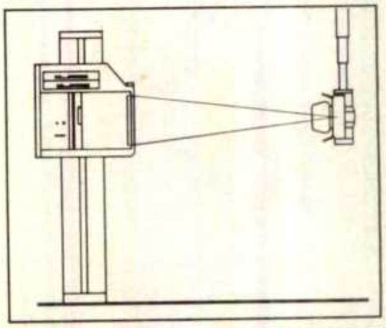

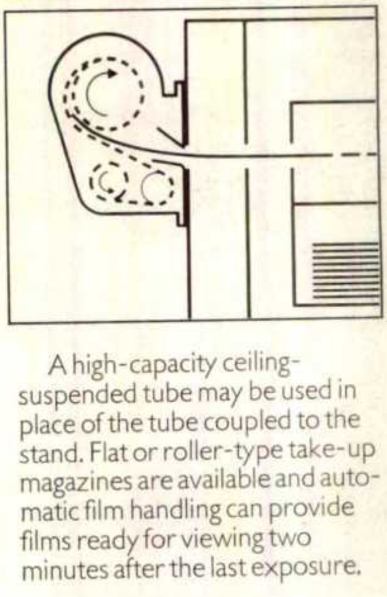

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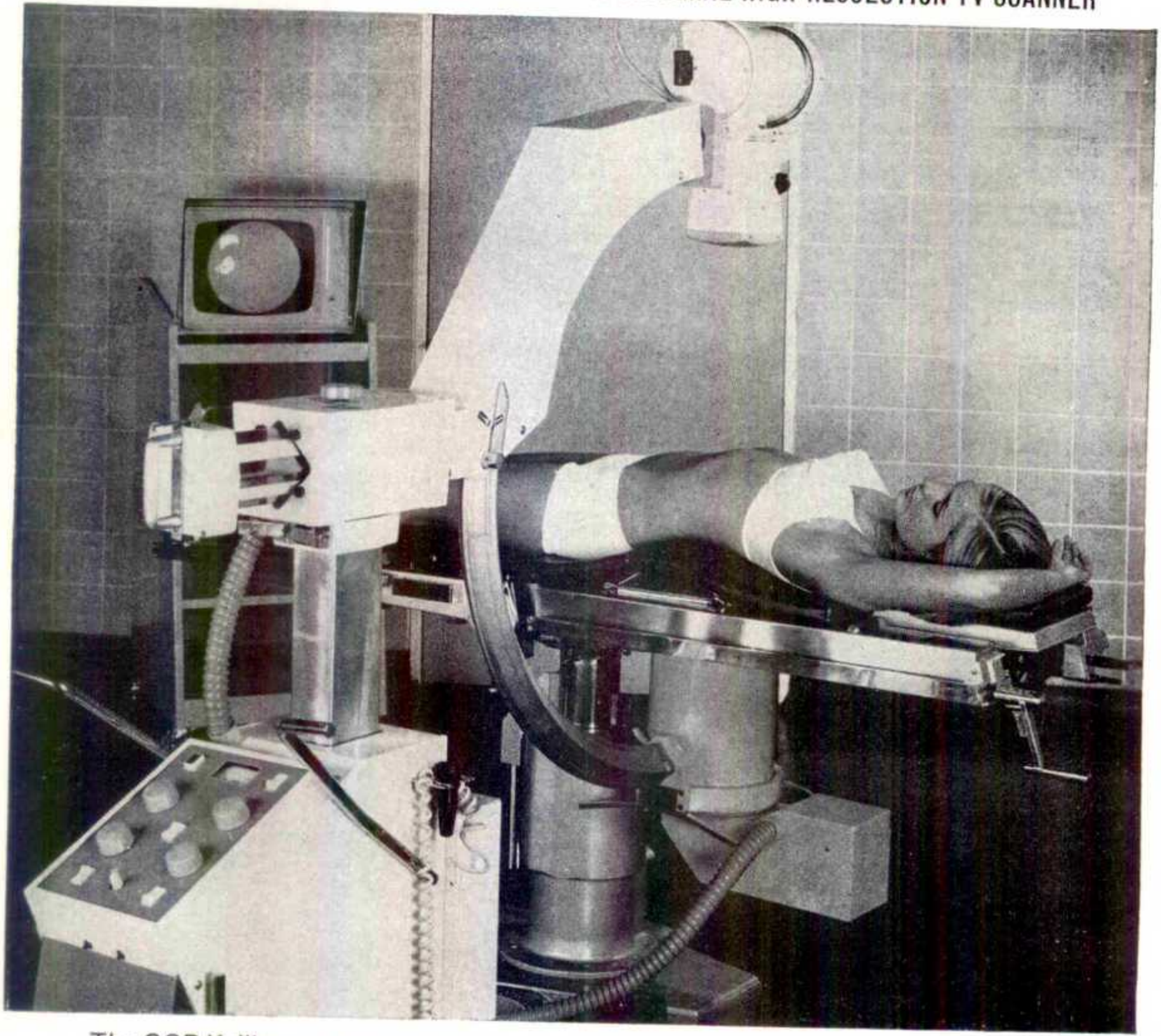

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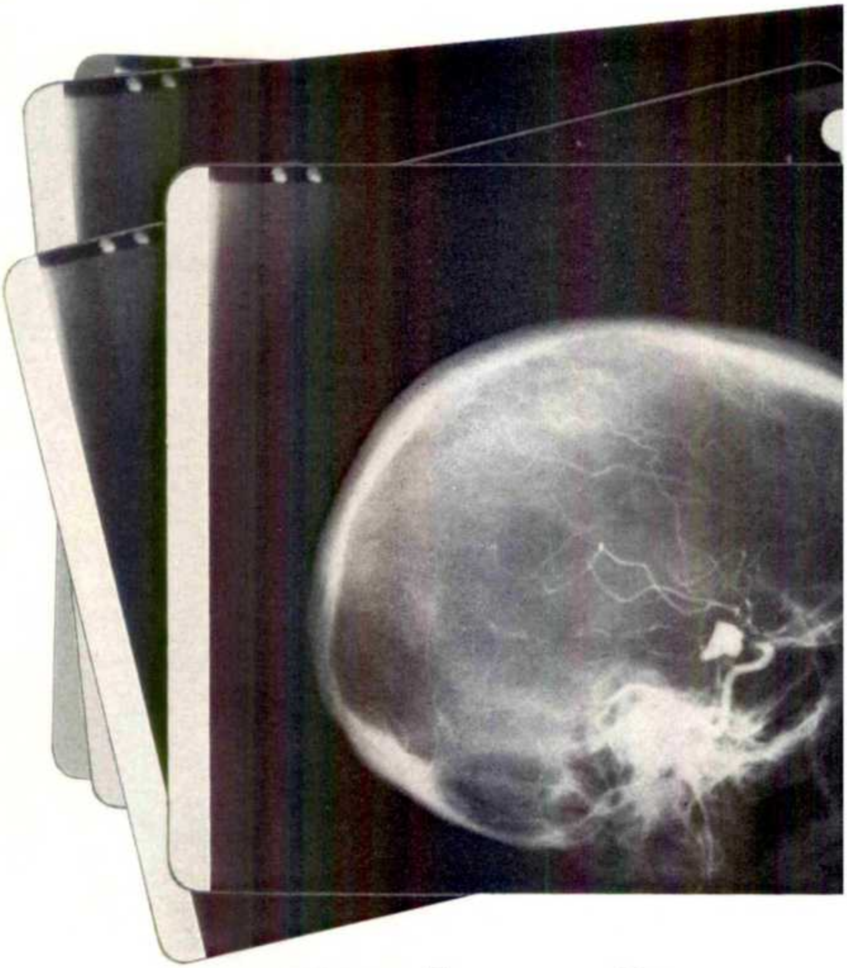

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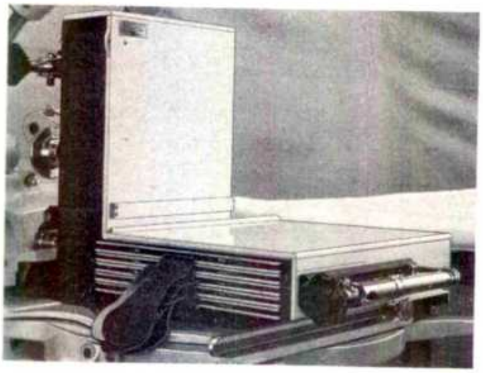

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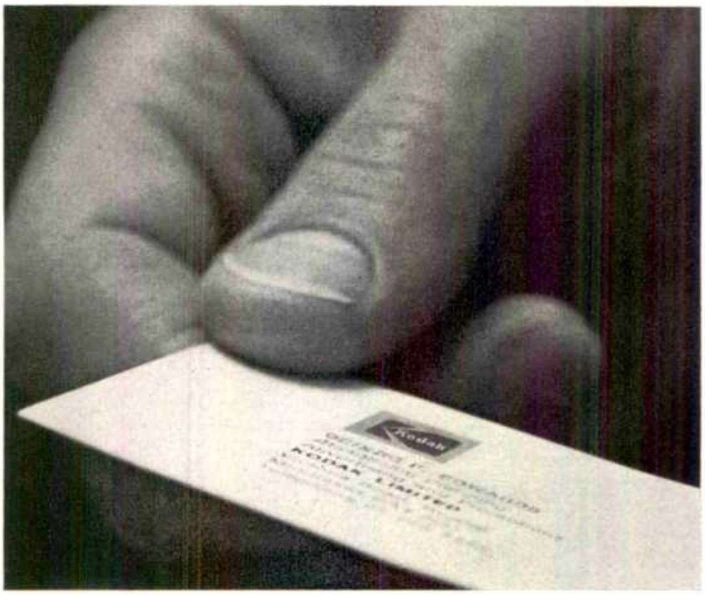

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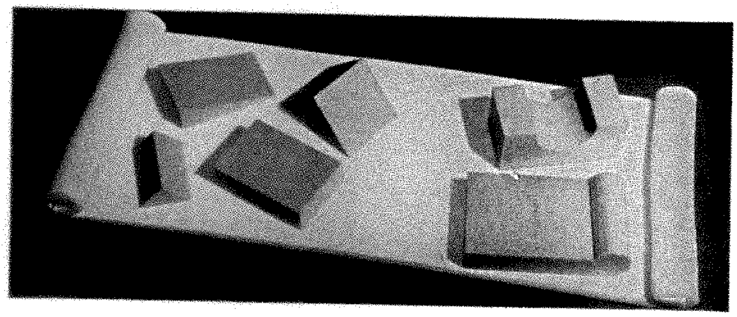

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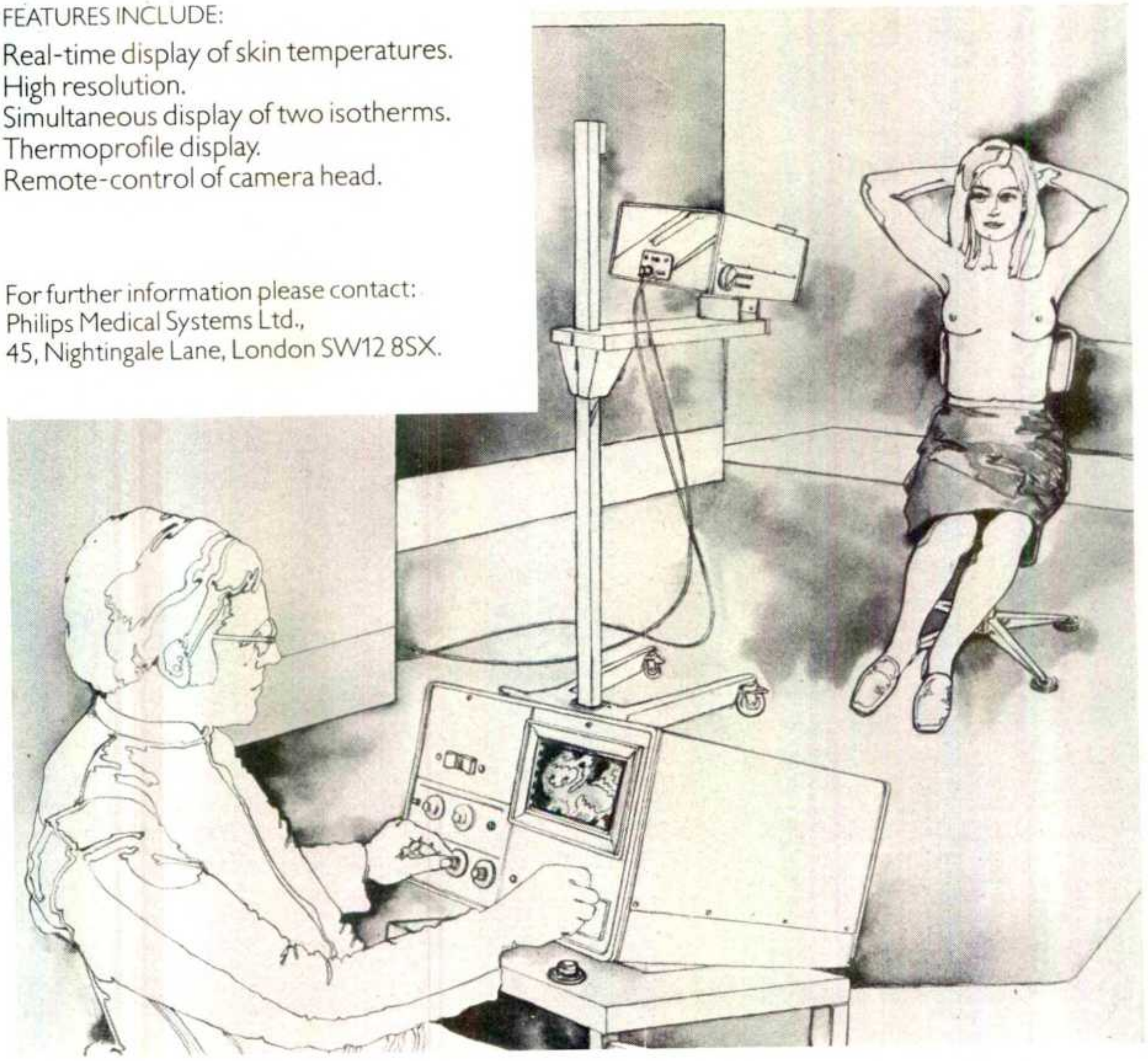

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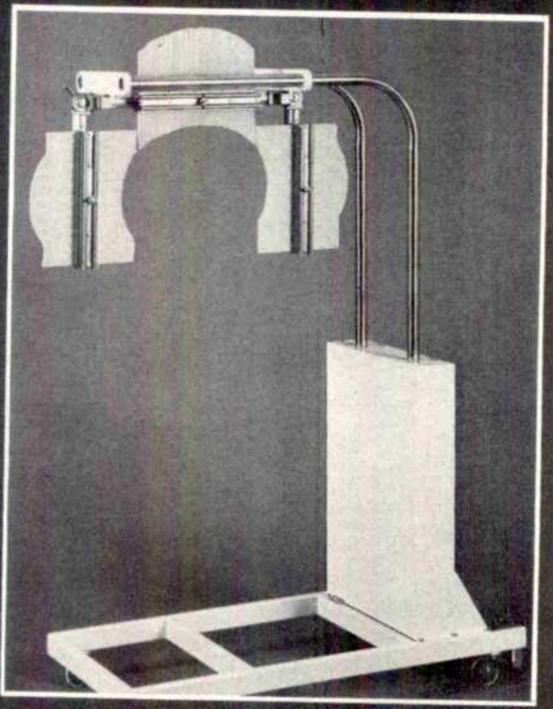

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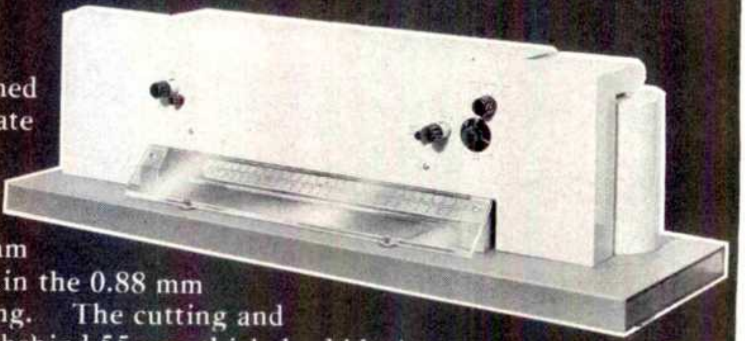

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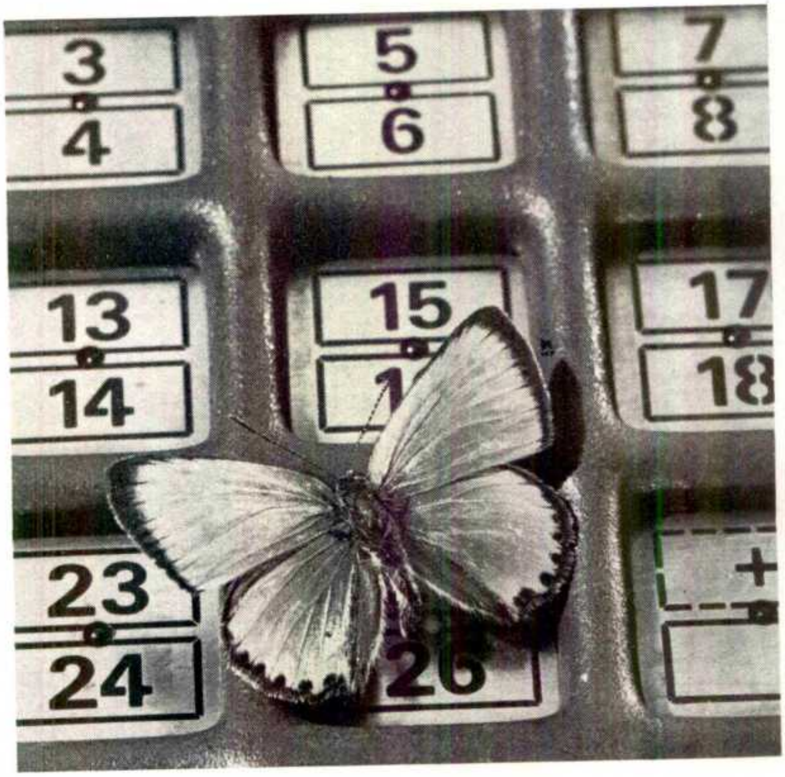

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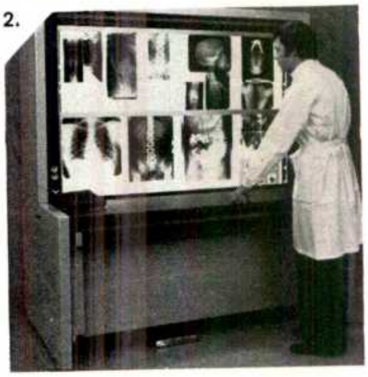

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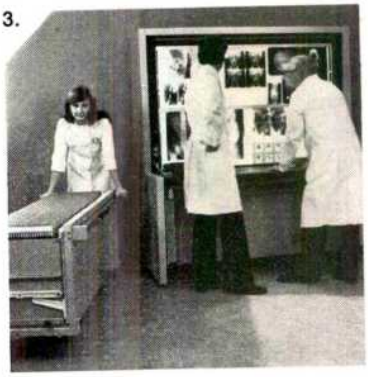

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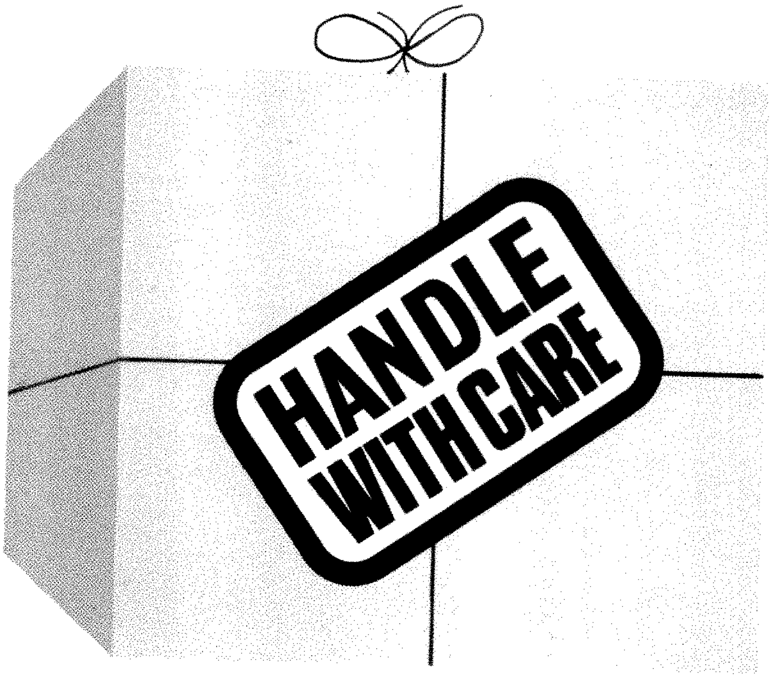

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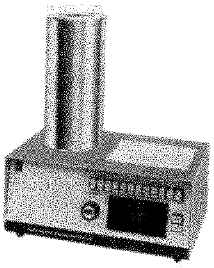

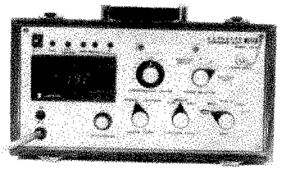

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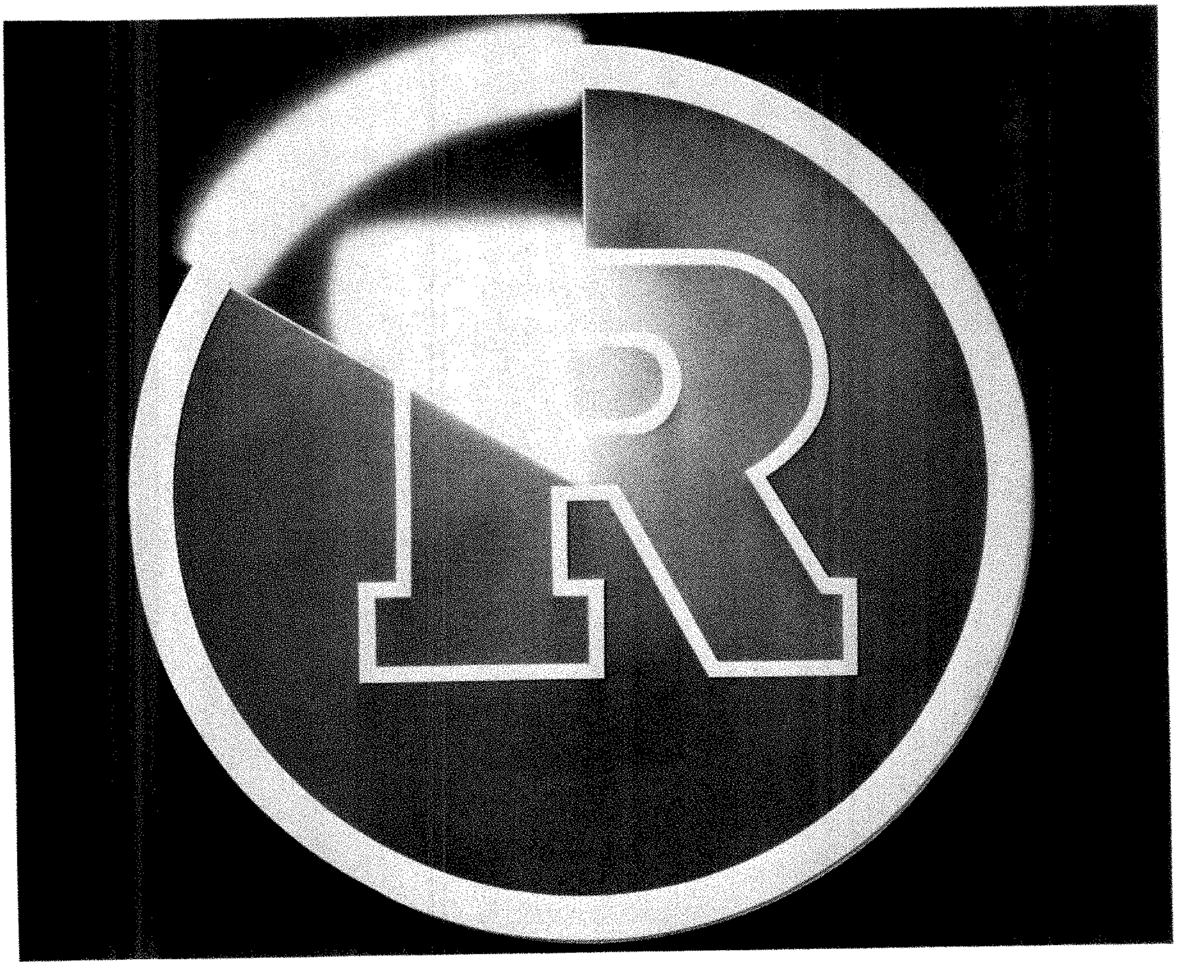

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R. H. Whitehouse

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M. J. R. Healy

Medical Research Council Clinical Research Centre, Harrow, England

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National Children's Bureau, London, England

January/February 1976, vi+100 pp. £9·00/$22.25
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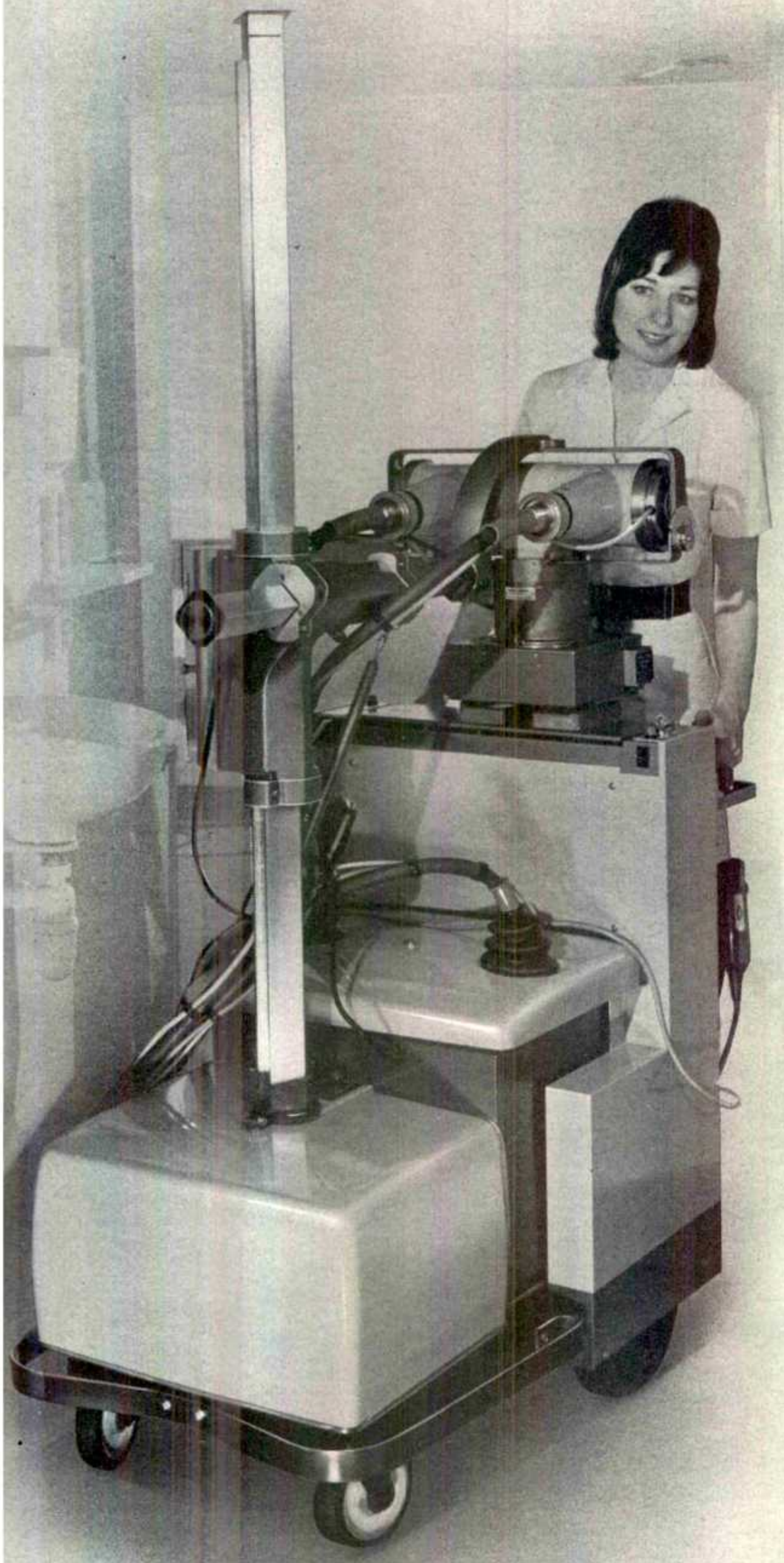

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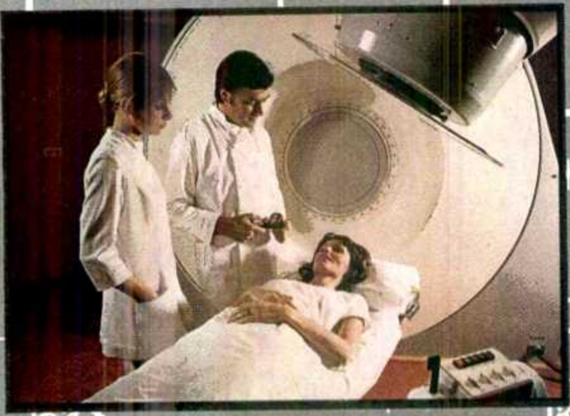

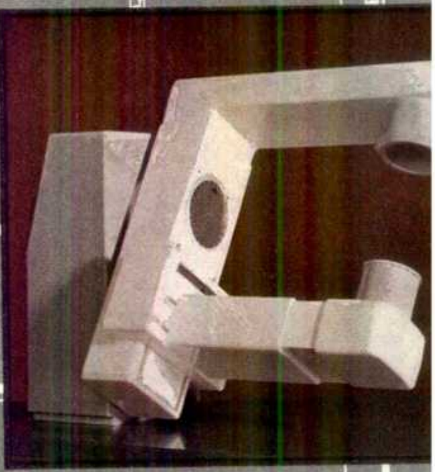

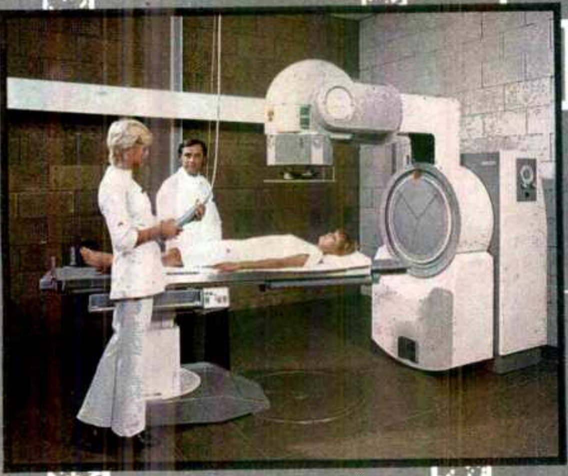

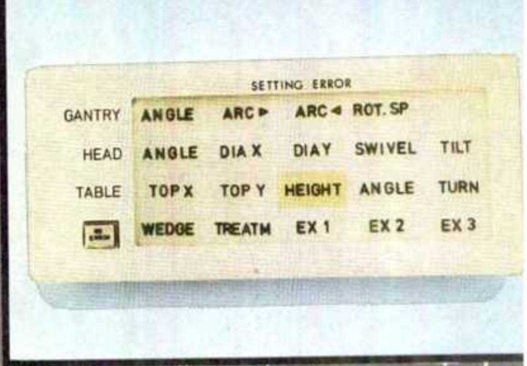
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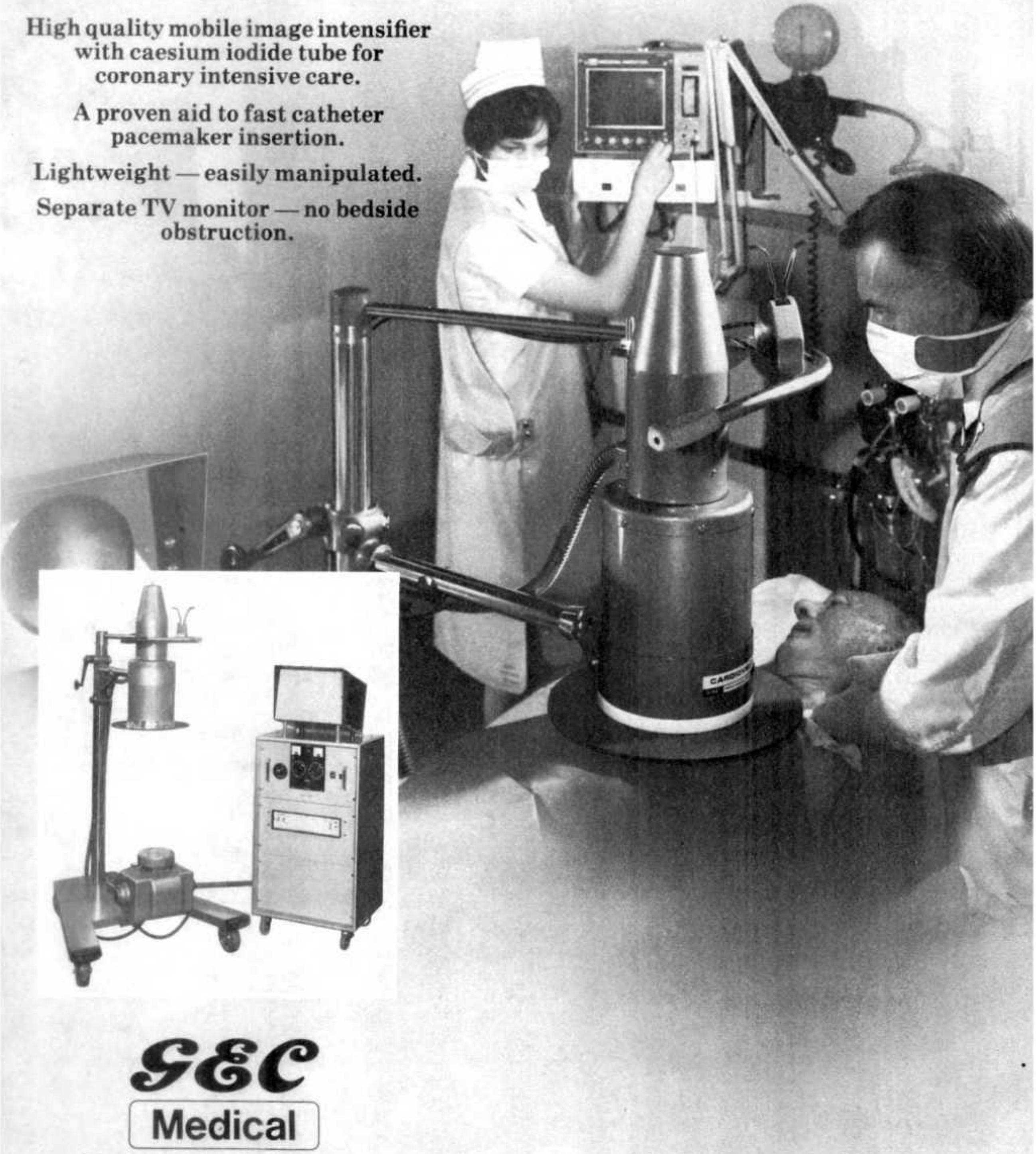

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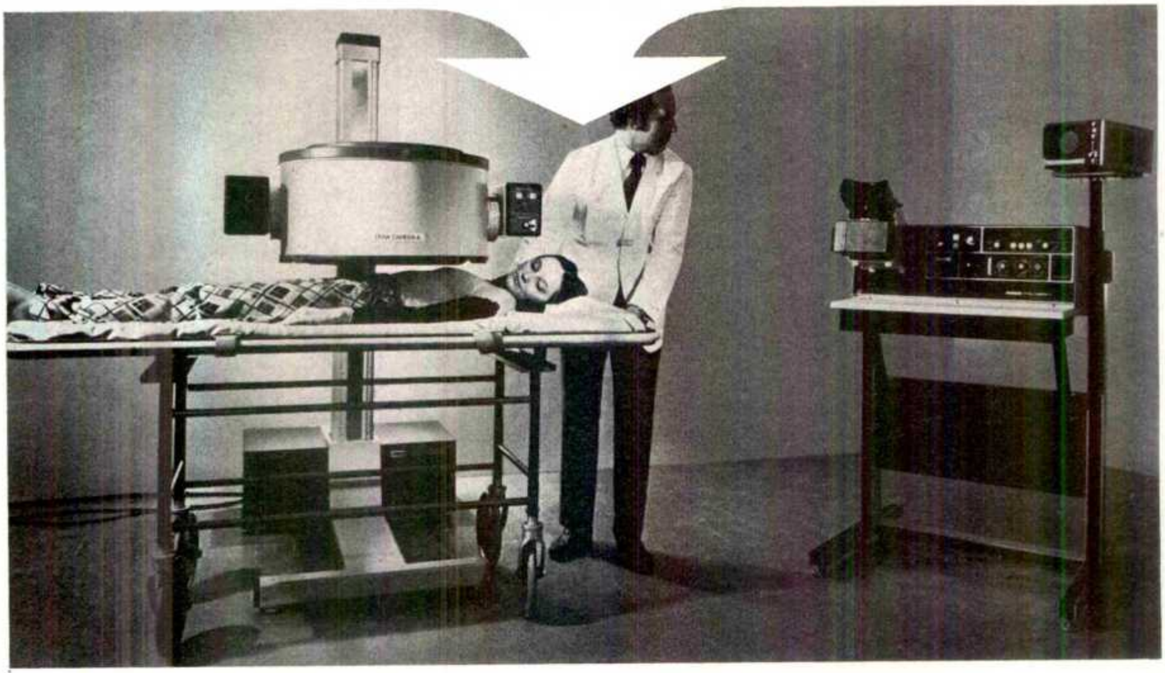

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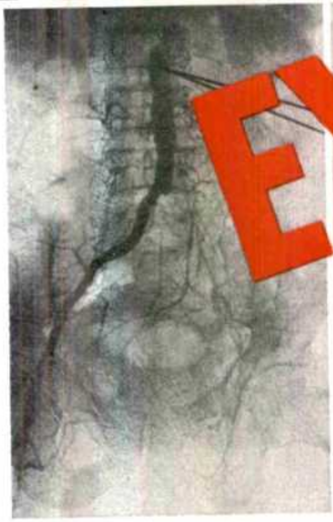

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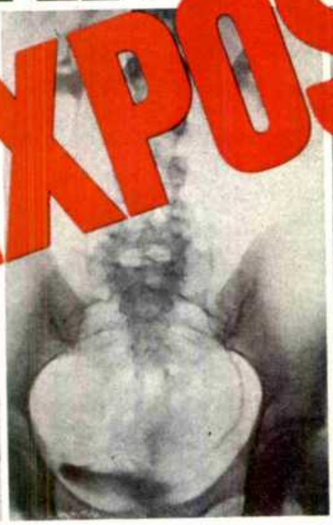

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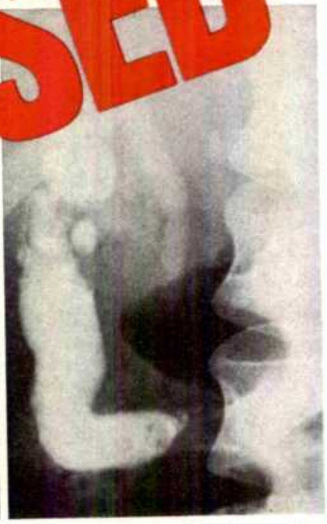

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1976, *British Journal of Radiology*, *49*, 103–104
VOLUME 49 NUMBER 578 FEBRUARY 1976

The British Journal of Radiology

Radiology now

Academic radiology*

The argument put forward for establishing academic posts in diagnostic radiology in this country is one of enlightened self-interest: medical students, if they have radiologists to teach them, will themselves choose to become radiologists. Since undergraduate education is a function of universities, it follows that we must have radiologists in university posts. Thus far the argument provokes little disagreement. It has been forcefully presented by others (Windeyer, 1969; Faculty of Radiologists, 1969) and has recently been passionately restated by Bull (1974). The correspondence which he stimulated (*e.g.* Bligh, 1974; Craig, 1974; Palmer, 1974) suggests that the need is widely recognized, at least by radiologists. Academic radiology has, of course, wider horizons, vividly apparent to any visitor to North American or Scandinavian departments with their splendid records of achievement in clinical investigation as well as in research and teaching. Self-interest dictates that we encourage the establishment of departments to assess, for example, the cost-effectiveness of the procedures we perform (McNeil *et al.*, 1975). We are not, of course, compelled to conclude that we need university employees to teach and to carry out research; there are many Health Service radiologists with outstanding academic records. Nonetheless, we must accept that, for most, service obligations frustrate such ambitions.

What kind of university radiologists, then, do we want? Should they be professors or of more humble rank? We seem to want professors. Do we wish to see academic units? This too seems to be agreed. Clearly research is important and this implies a need for accommodation and personnel. Should academic radiologists be responsible for all aspects of teaching, postgraduate as well as undergraduate? Here, incredibly, we begin to disagree, some taking the bizarre view that academic radiologists are remote from the practical training required by practical Health Service radiologists. How much power should we give to our academic radiologists? Should they be responsible for the clinical standards of the departments in which they work? Now we move into more turbulent waters.

Academic radiology is, without question, best practised as a collective enterprise in an environment in which teaching, research, and high standards of patient care are encouraged. We must be careful that by attempting to establish chairs in radiology within Health Service departments, but without power, we do not create academic ghettoes. Comparisons with academic departments of medicine or surgery are not valid. They function as totally independent units, setting their own standards, recruiting their own personnel, in a way that small academic units of radiology within Health Service departments cannot. It would be more appropriate to choose as our models other kinds of university departments which function in teaching hospitals: microbiology, chemical pathology, morbid anatomy. These departments are usually staffed by university personnel with a professor at their head, their services, in a sense, being leased by the Health Service. An alternative arrangement, in which most permanent staff are part of the Health Service with a professor as director, can also succeed (Bligh, 1974). The question of leadership is vital. Where few academic traditions exist, the professor must be able to establish teaching and research as part of the normal function of a major teaching hospital department. He is hamstrung if general departmental policy is beyond his control. Decisions, for instance, on systems of film filing are important if retrospective research is to be undertaken or teaching films are to be readily obtained. Control of radiographic standards is an even more obvious example.

Mackintosh (1975) outlines two principles on which the Health Service operates. No-one must hold authority over senior consultants. His second principle, which we are not discussing, is that no-one must be sacked. The Health Service fears administrative pyramids for doctors; universities are less apprehensive. We should remember that professors are chosen after much thorough inquiry. They compete against other applicants. Though imperfect, the rules are those of selection rather than inheritance. The arrival of senior consultants in positions of administrative authority may owe more to longevity than talent.

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But can we establish academic departments of radiology, serving the needs of teaching hospitals, administered and staffed by university personnel? The unified structure, with its implications of a common philosophy, is attractive. The system works in North America and Scandinavia. In Britain we would probably require a compromise. The appointment of a professor as director of a department staffed by Health Service consultants, but with a sizeable university component, is less desirable, for the seeds of conflict exist. However, unless we are prepared to change our attitudes and appoint our professors as heads of departments in *teaching* (the word requires emphasis) hospitals, we cannot anticipate the kind of advances in academic radiology which we claim that we want. We cannot ask professors to function as strait-jacketed members of groups which they are expected to inspire. The future for academic radiology lies with us all. Collectively, we must decide how much we are prepared to commit ourselves to safeguard that future.

Ten years ago Miller (1966) reviewed events in medical education and hospital services since Flexner's recommendations of half a century before. Flexner (1910), after a penetrating examination of medical teaching in North America, advocated the establishment of university hospitals, controlled and staffed by individuals committed to the advancement of teaching and research. In Britain, alas, he found "conservatism, vested interests, absence of true university ideals, lack of resources, lack of leadership and excessive dependence on tedious committee procedure" (Flexner, 1925). Noting the enormous advances in medical standards which resulted from the implementation of Flexner's concepts in North America, Miller too concluded that our failure to do so in this country resulted from "national parsimony, evident in affluent as well as difficult times, and from a complacent acceptance of the amateurish and second-best". Today the universities and the Health Service are more parsimonious than they were even a decade ago. With standards rising elsewhere, what was second-rate then is third-rate today. Soon, only complacency may remain. In the present state of economic shipwreck, does the plight of academic radiology really matter? For those who care about British radiology, which in its time has known a Twining and a Barclay, the question is not trivial. And, now is the time to hold the discussion. With the universities and the Health Service bracing themselves against a long and bitter winter, we should ask ourselves what kind of environment we would like to see when the ice melts. Inevitably we shall see much change. Now is a good time to make plans.

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REFERENCES

BLIGH, A. S., 1974. Place of diagnostic radiology in medicine. *British Medical Journal, 3*, 684.

BULL, J. W. D., 1974. What is diagnostic radiology's place in medicine? *British Medical Journal, 3*, 394–400.

CRAIG, O., 1974. Place of diagnostic radiology in medicine. *British Medical Journal, 4*, 343.

FACULTY OF RADIOLOGISTS, 1969. Pamphlet: *Vocational training and registration in radiology in the light of the report of the Royal Commission on Medical Education*, pp. 1–12.

FLEXNER, A., 1910. Medical Education in the United States and Canada. In *Carnegie Foundation for Advancement of Teaching. Bulletin No. 4.*

1925. *Medical Education* (Macmillan, New York).

MACKINTOSH, J. P., 1975. Our current discontents. *British Journal of Hospital Medicine, 14*, 106.

McNEIL, B. J., VARADY, P. D., BURROWS, B. A., and ADELSTEIN, S. J., 1975. Cost effectiveness in renovascular disease. *New England Journal of Medicine, 293*, 216–221.

MILLER, H., 1966. Fifty years after Flexner. *The Lancet, 2*, 647–654.

PALMER, P. E. S., 1974. Place of diagnostic radiology in medicine. *British Medical Journal, 4*, 654–655.

WINDEYER, B., 1969. Education in radiology. *Clinical Radiology, 20*, 241–246.

1976, *British Journal of Radiology*, *49*, 105–110 FEBRUARY 1976

Bone disease in long-term haemodialysis: the association of radiological with histological abnormalities

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(*Received June, 1975*)

ABSTRACT

The radiological findings in the skeletal surveys of 70 patients receiving long-term haemodialysis for chronic renal failure have been correlated with histological findings in a specimen obtained by biopsy of the iliac crest. Many significant associations were found, and the ones presented are those thought to be most useful in the interpretation of the radiological abnormalities. The main conclusions are that fractures and severe medullary rarefaction appear to be most commonly the result of osteomalacia; subperiosteal erosions are associated with the more severe grades of osteitis fibrosa; cortical striations and sclerosis are associated with an increased amount of osteoid, and sclerosis is diagnosed more frequently by radiological means than by iliac-crest biopsy.

Patients on regular haemodialysis often suffer from a bone disease attributed to osteomalacia, hyperparathyroidism and osteoporosis occurring either alone or in combination. As the prospect of treating these diseases improves, accurate diagnosis by a non-invasive technique becomes increasingly important. The X-ray appearances of each of these conditions have been described in patients with a single proved metabolic disorder. Steinbach *et al.* (1961) have described the radiological features of hyperparathyroidism, Steinbach and Noetzli (1964) the radiological features of osteomalacia and Feist (1970) the radiological features of osteoporosis. From these descriptions it has been assumed that certain radiological abnormalities are specific for certain diseases. For example, it is generally assumed that subperiosteal erosions in the phalanges indicate hyperparathyroidism and that Looser zones indicate osteomalacia. On the other hand certain radiological features, *e.g.* decreased radiodensity, pathological fractures and osteosclerosis have been known to occur in more than one primary disease, and thus it is difficult to know what significance to attach to them.

With the increasing use of iliac-crest biopsy it is now possible to use histological findings to determine the accuracy of radiological signs in diagnosing the nature of the bone changes. In this paper we have made such correlations in patients with azotaemic renal disease being treated by long-term haemodialysis.

MATERIALS AND METHODS

Seventy patients receiving intermittent haemodialysis for azotaemic renal disease were chosen on the basis of having had a bone biopsy within six months of a skeletal survey. The skeletal surveys were done at six monthly, or yearly intervals and only patients who had no significant change in the X-ray appearance immediately before or immediately following the biopsy were selected. It was a heterogeneous group in terms of the primary renal disorder, age, sex and duration of dialysis. The ages of the patients ranged from 19 to 61 years with a mean of 41 years, time on haemodialysis was up to eight years with a mean of two years, and there were 24 females and 46 males.

The radiographic features are listed in Table I. All but three of these are well known and have been described by Simpson *et al.* (1973a). Juxta-articular and medullary change are not such well-known features but are also described in the same publication. Cortical striations are another of the less well-known radiological features and have been described by Meema and Meema (1972). The last three abnormalities are illustrated (Fig. 1).

The methods used for quantitative histological analysis have been previously described (Ellis and Peart, 1972, 1973). The histological features used for correlation are listed in Table II. Osteomalacia is defined histologically as an excess of osteoid with more than four bi-refringent lamellae in the osteoid seams and decreased calcification fronts. The latter two features are important as excess osteoid may be found in conditions other than osteomalacia, and is a common finding in osteitis fibrosa as a result of osteoblastic activity over an increased proportion of the bone surface.

The association between each radiological and histological feature was examined using the chi-squared test, or Fisher's exact test where numbers were small. Most of the radiological signs were originally graded according to severity, but as there were too few cases in each grade, the analyses presented here are concerned only with the presence

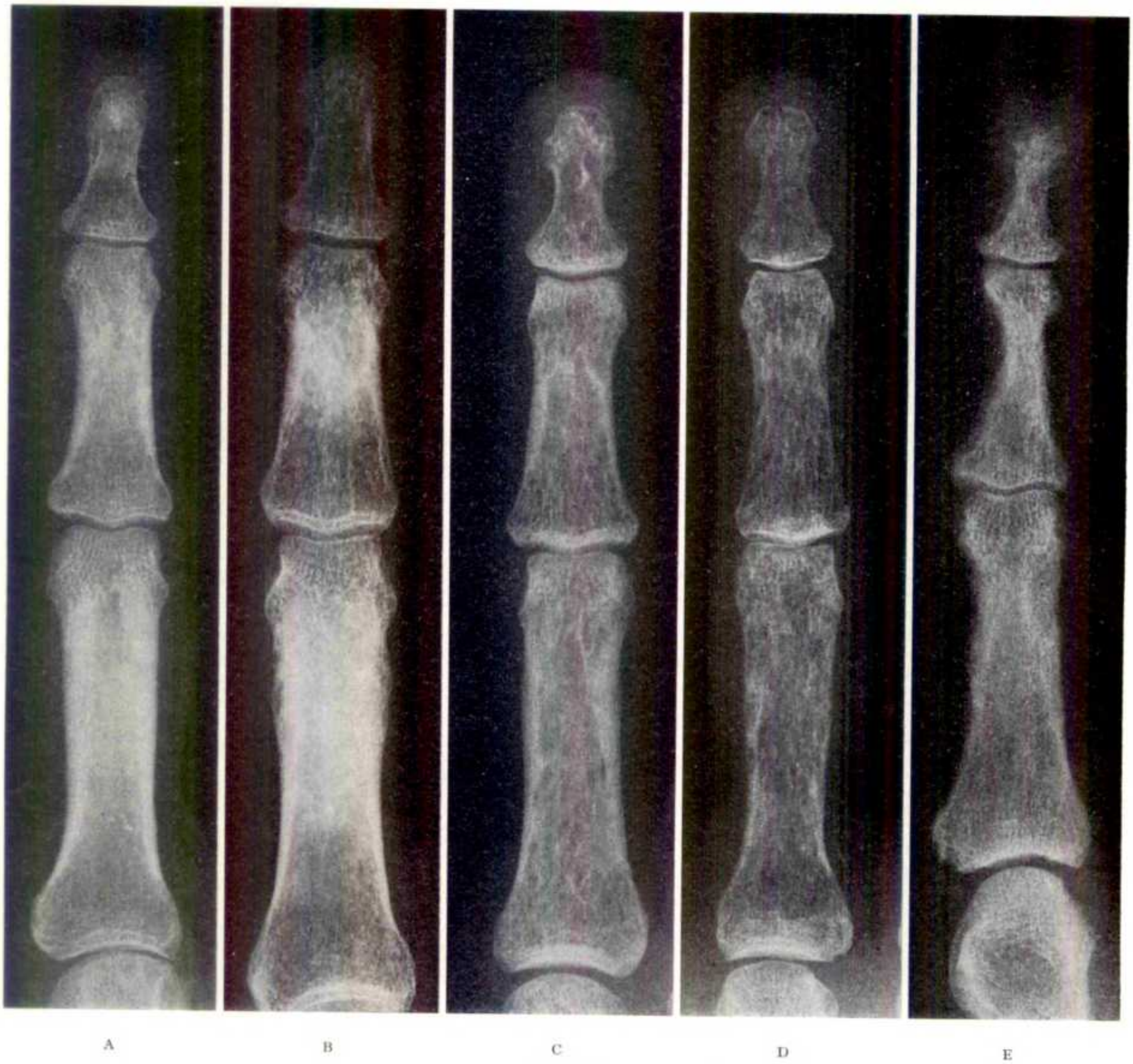

FIG. 1.

Radiographic changes in phalanges

(A) Normal appearance. (B) Juxta-articular rarefaction: graded 0–4 with increasing severity, this is Grade 3. (C) Medullary rarefaction: a focal osteolytic process in the medullary cavity with exaggerated trabeculae, also graded 0–4, this is Grade 3. (D) Cortical striations: oval or linear areas of rarefaction in the compact bone of the cortex with an intact subperiosteal surface. This also shows Grade 4 medullary rarefaction. (E) Subperiosteal erosions.

or absence of radiological features. The grades are included only for medullary change in the hands.

Although the whole series consisted of 70 patients, there were three with incomplete data. The total number in each analysis therefore varies from 67 to 70.

RESULTS

Most of the results are presented in Table III. We think that the most important findings are the following:

(1) Fractures were associated with histological osteomalacia. Of 42 patients with osteomalacia 16 (38 per cent) had fractures, whereas of the 27 with no osteomalacia only 2 (7 per cent) had fractures.

(2) The higher grades of medullary rarefaction in the hands were also found to correlate with osteomalacia. Grades 3 and 4 were found in seven (17 per cent) out of 42 patients with

TABLE I

THE RADIOLOGICAL ABNORMALITIES

Subperiosteal erosions in phalanges
Erosions in other sites (Greenfield, 1972)
Abnormal mottling in the skull vault
Fractures or Looser zones (analysed according to site and whether new, old unhealed or old healed)
Vertebral collapse
Sclerosis—(a) Spine
  (b) Hands (juxta-articular)
  (c) Femoral heads
  (d) Whole skeleton
Juxta-articular rarefaction—(a) Hands
  (b) Feet
Medullary rarefaction —(a) Hands
  (b) Feet
Metacarpal cortical thickness (Morgan *et al.*, 1967)
Ratio of cortical to surface area in the second metacarpal (Exton-Smith *et al.*, 1969)
Abnormal vertical striations in the cortex of metacarpals and phalanges – cortical striations

TABLE II

THE HISTOLOGICAL ASSESSMENTS

Total bone (N = 16·6–28·8%)
Total mineralized bone (N = 16·5 – 28·6%)
Percentage mineralization ($N > 98{\cdot}2\%$)
Total osteoid ($N < 0{\cdot}45\%$)
Osteomalacia based on:
(a) Excess osteoid with > four birefringent lamellae in seams
(b) Decreased calcification fronts
Osteitis fibrosa based on:
(a) Surface resorption and tunnelling by multinucleated osteoclasts
(b) Marrow fibrosis with increased osteoblastic activity
(c) Woven bone formation

TABLE III

THE ASSOCIATION OF THE MAIN RADIOLOGICAL WITH HISTOLOGICAL FINDINGS

Histology

Radiology	Total bone			Mineralized bone			Osteoid excess			%age Mineralization			Osteomalacia			Osteitis fibrosa		
	High[1]	Low[1]		High[1]	Low[1]		+	−		Normal[1]	Low[1]		+	−		+	−	
	(20) %	(8) %	p[2] <	(13) %	(11) %	p[2] <	(57) %	(13) %	p <	(10) %	(59) %	p <	(42) %	(27) %	p <	(55) %	(15) %	p <
Erosions (22) in the hands	70	25	0·001	80	18	0·001	39	0	0·01	0	34	0·05	33	30	NS	34	20	NS
Fractures (14) in the ribs	5	37	0·05	8	45	NS	22	8	NS	0	24	NS	29	7	0·05	20	20	NS
Fractures (18) anywhere	20	37	NS	15	45	NS	31	8	NS	10	29	NS	38	7	0·005	27	20	NS
Sclerosis (22) in the spine	65	37	0·001	62	27	0·01	36	8	0·05	10	34	NS	36	22	NS	35	20	NS
Sclerosis (34) anywhere	75	63	0·005	69	64	NS	58	8	0·001	10	54	0·05	62	26	0·005	55	27	0·05
Cortical (17) striation	25	12	NS	15	36	NS	30	0	0·05	0	27	NS	29	15	NS	22	7	NS
Medullary (7) rarefaction > Grade 2	10	0	NS	0	9	NS	12	0	NS	0	12	NS	17	0	0·05	11	7	NS

The figures in brackets are the absolute numbers. NS (not significant) indicates $p > 0{\cdot}05$.

[1] See Table II for normal range.

[2] In these columns X^2 and hence p were derived by correlating the high values with the low *or normal* values.

osteomalacia, and in none of those with no osteomalacia.

(3) A significant association between subperiosteal erosions and osteitis fibrosa was found only at the higher grades of osteitis fibrosa. Altogether 55 patients showed some histological evidence of osteitis fibrosa and 19 (34 per cent) of these had erosions. This was not significantly different from the finding of three patients (20 per cent) with erosions among the 15 with no osteitis fibrosa. When the grades of osteitis fibrosa were considered it was found that there were 19 patients with a higher grade than 2, of whom 14 (74 per cent) had erosions. This is a significant finding ($p < 0{\cdot}001$) when contrasted with only eight (16 per cent) with erosions out of the 51 with lesser grades of or no osteitis fibrosa.

(4) Cortical striations were invariably associated with excess osteoid, all 17 patients with cortical striations having an increased amount of osteoid.

(5) Radiological sclerosis showed an association with most of the histological parameters, an interesting one being the association with an increased amount of osteoid. Of 57 patients with osteoid excess 33 (58 per cent) had sclerosis, whereas of the 13 with no osteoid excess only one (8 per cent) had sclerosis. There was a poor association with the total amount of mineralized bone, and seven (64 per cent) out of the 11 with ***abnormally low*** levels of mineralized bone showed sclerosis. Also there were only 15 patients who had any histological evidence of sclerosis (a high level of total bone) out of the 34 with sclerosis radiologically.

The following radiological features were not related to any histological abnormality: vertebral collapse, metacarpal cortical thickness, ratio of cortical area to surface area in the second metacarpal, juxta-articular change and sclerosis in any localized site other than the spine.

Discussion

Fractures

Previous authors have expressed different opinions about the aetiology of fractures in renal bone disease. They have been attributed to osteoporosis (Bishop, 1973) and to hyperparathyroidism (Platts *et al.*, 1973). However, we have suspected that osteomalacia is the most important aetiological factor as in many cases the fractures show the typical features of Looser zones and their healing may be delayed, like the fractures found in dietary osteomalacia (Simpson, Young and Clark, 1973b). We now have histological support for this hypothesis.

Our results show that fractures were present more often in patients with low or normal than in those with high total bone, but as these low or normal values were present in only one-third of the patients with fractures, osteoporosis is obviously not often the causative factor. No significant association has been found between the occurrence of fractures and histological osteitis fibrosa. On the other hand 87 per cent of patients with fractures had osteomalacia and there is a statistically significant association with this histological finding.

Therefore, most patients with fractures had osteomalacia, but only 38 per cent of those with osteomalacia had fractures. As there are no other radiological features which are in any way specific for osteomalacia, this diagnosis must most frequently be determined by biopsy.

Altogether 18 of our patients had radiological evidence of unhealed fractures. In 11 of these patients one or several Looser zones were present when the analyses were repeated. Correlating Looser zones rather than fractures with the histological parameters, the same significant associations were found. This suggests that unhealed fractures and Looser zones are both caused by the same pathological process (osteomalacia) and that one is probably a stage in the development of the other. The finding of Ball and Garner (1966) that fractures and Looser zones in patients with osteomalacia have the same histological features supports this hypothesis.

Sclerosis

Histological sclerosis is defined as a total bone in excess of 28·8 per cent (Normal mean × 2 SD, Ellis and Peart, 1972). Radiological sclerosis might reasonably be expected to be due to an increase in mineralized bone, as non-mineralized bone is not known to be radiologically distinguishable from other soft tissues. However, except for sclerosis in the spine, no significant association was found between high values of mineralized bone and radiological sclerosis, the former occurring in only 27 per cent of cases with the latter. This may possibly be due to the fact that sclerosis is of patchy distribution, and may be underdiagnosed histologically as only a small area of iliac crest is available for analysis.

There is a significant association between high total bone values and radiological sclerosis, the former being present in 45 per cent of cases with this radiological feature. But the histological measurement which is most strikingly associated with radiological sclerosis is excess osteoid, 97 per cent of patients with radiological sclerosis having this feature.

Radiological sclerosis is also significantly associated with osteitis fibrosa and osteomalacia, the former occurring in 81 per cent and the latter in 76 per cent of patients with radiological sclerosis.

This clear association between radiological sclerosis and an increased amount of uncalcified osteoid is difficult to explain. Previous authors who have made the same observation (Eugenidis, Attila and Hass, 1972) have suggested that an excess of uncalcified osteoid may itself increase radiodensity. Although it is true that "uncalcified" osteoid may have an appreciable content of calcium (Eastwood *et al.*, 1974) it appears on histological preparations to be small compared with uncalcified bone, so we think this is an unlikely explanation. We presume that there is an excess of mineralized bone in the sclerotic areas which is not necessarily reflected in the iliac crest; the latter has a slower turnover than some of the sites in which sclerosis is common, such as the vertebral bodies (Kaye, 1964).

If sclerosis were associated only with hyperparathyroidism the obvious explanation would be an accumulation of mineralized woven bone in high turnover areas. However our findings suggest that osteomalacia is equally important in the development of sclerosis: an excess of woven bone is not a feature of non-azotaemic osteomalacia, so it can hardly explain this association. It may be that osteomalacia contributes to sclerosis in high turnover areas when there is an intermittent calcification defect; osteoid builds up during periods when mineralization defect is severe, protecting the bone in these areas from its usual high rate of resorption (Garner and Ball, 1966). If there is a temporary improvement in mineralization, the large amount of osteoid in these areas will permit rapid mineralization and build up of mineralized bone. We have no direct evidence that the mineralization defect in uraemia is intermittent but the incidence of osteomalacia does vary surprisingly from centre to centre (Siddiqui and Kerr, 1971), and it may even be absent from anephric patients who have no known source of 1.25-Di-Hydroxycholecalciferol (Bordier *et al.*, 1973). It may well be, therefore, that variable levels of other vitamin D metabolites (*e.g.* 25-Hydroxycholecalciferol which has a seasonal fluctuation in serum level – McLaughlin *et al.*, 1974) can account for an intermittent calcification defect.

Cortical Striations

This radiographic feature is seen as an exaggeration in the number and/or size of the transradiant lines in cortical bone. Its presence has been ascribed to various pathological features. Genant *et al.* (1973), found it in hyperparathyroidism, Meema and Schatz (1970) in thyrotoxicosis and Jones (1969) in disuse osteoporosis. We found that cortical striations were present only in patients with excess osteoid. It was not found to be significantly associated with any of the other histological parameters, which implies that it is not specific for any one condition but is found where osteoid content of bone is increased—in osteomalacia or osteitis fibrosa. This characteristic is sought by us in the phalanges and metacarpals. Our technique of assessing this measurement (Fig. 1) was less rigid than that of Meema and Meema (1972) who confined their assessment to the mid shaft of the second metacarpal. Using their criteria, only two of our patients had positive findings.

Subperiosteal erosions

The pathological significance of subperiosteal erosions is one of the least controversial aspects of this topic. Previous workers, Cohen *et al.* (1970), Byers and Smith (1971), Doyle *et al.* (1972), Meema *et al.*, (1972) and Pugh (1951) all agree that they are a manifestation of hyperparathyroidism. Our work supports this, but we found a significant association only when the more severe histological grades of osteitis fibrosa were considered.

The radiological accuracy might have been increased by using industrial film to take fine detail radiographs and by examining them under magnification (Meema *et al.*, 1972), or using a direct magnification technique (Calenoff and Norfray, 1973). But we have preferred a simple radiographic method using non-screen film, to keep the technique constant and allow comparisons to be made with earlier groups of patients. We found subperiosteal erosions to be associated with histological sclerosis and excess osteoid, but not with osteomalacia.

Juxta-articular change

This abnormality showed a poor association with all the histological measurements.

Medullary change

The more marked grades of this abnormality were found to be significantly associated with histological osteomalacia. Though this was contrary to our anticipation of an association with osteoporosis, it is compatible with as yet unpublished data from this centre showing that medullary rarefaction is associated with clinical and biochemical indices of osteomalacia.

CONCLUSION

The subjectivity of radiological assessment, the small and sometimes unrepresentative area available for histological analysis, and the fact that individual patients often have more than one basic pathological process are but some of the facts contributing to the difficulties encountered in drawing conclusions from comparison of histological and radiological findings in a group such as this. Nevertheless, certain facts emerge:

(1) Fractures and medullary rarefaction are usually associated with osteomalacia.
(2) Cortical striations and sclerosis are associated with excess osteoid either due to osteomalacia or hyperparathyroidism.
(3) Subperiosteal erosions are associated with the more severe grades of osteitis fibrosa.
(4) Radiology is more sensitive than iliac crest biopsy in the diagnosis of sclerosis.

ACKNOWLEDGMENTS

We should like to thank all the doctors who have made this work possible by performing the iliac crest biopsies.

REFERENCES

Ball, J., and Garner, A., 1966. Mineralisation of woven bone in osteomalacia. *Journal of Pathology and Bacteriology, 91,* 563–567.

Bishop, M. D., 1973. Plasma biochemistry in haemodialysed patients. *Lancet, 2,* 1328–1329.

Bordier, P. J., Tun Chot, S., Eastwood, J. B., Fournier, A., and De Wardener, H. E., 1973. Lack of histological evidence of Vitamin D abnormality in the bones of anephric patients. *Clinical Science, 44,* 33–41.

Byers, P. D., and Smith, R., 1971. Quantitative histology of bone in hyperparathyroidism. Its relation to clinical features, X-ray and biochemistry. *Quarterly Journal of Medicine, 40,* 471–481.

Calenoff, L., and Norfray, J., 1973. Magnification digital roentgenography: a method for evaluating renal osteodystrophy in hemodialyzed patients. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 118,* 282–292.

Cohen, M.E. L., Cohen, G. F., Ahad, V., and Kaye, M., 1970. Renal osteodystrophy in patients on chronic haemodialysis. A radiological study. *Clinical Radiology, 21* 124–134.

Doyle, F. H., Aung, Than, Carroll, R. N. P., Williams, E. D., and Shackman, R., 1972. Bone resorption in chronic renal failure: a comparison of radiological and histological assessments. *British Medical Bulletin, 28,* 225–227.

Eastwood, J. B., Bordier, E. M., Clarkson, E. M., Tun Chot, S., and De Wardener, H. E., 1974. The contrasting effects on bone histology of vitamin D and of calcium carbonate in the osteomalacia of chronic renal failure. *Clinical Science and Molecular Medicine, 47,* 23–42.

Ellis, H. A., and Peart, K. M., 1972. Quantitative observations on mineralised and non-mineralised bone in the iliac crest. *Journal of Clinical Pathology, 25,* 277–286.

1973. Azotaemic renal osteodystrophy: a quantitative study on iliac bone. *Journal of Clinical Pathology, 26,* 83–101.

Eugenidis, N., Attila, J. O., and Hass, H. G., 1972. Osteosclerosis in hyperparathyroidism. *Radiology, 105,* 265–275.

Exton-Smith, A. N., Millard, P. H., Payne, P. R., and Wheeler, Erica, F., 1969. Pattern of development and loss of bone with age. *Lancet, 2,* 1154–1157.

Feist, J. H., 1970. The biological basis of radiologic findings in bone disease. Recognition and interpretation of abnormal bone architecture. *Radiological Clinics of North America, 8,* 183–206.

Garner, A., and Ball, J., 1966. Quantitative observations on mineralised and unmineralised bone in chronic renal azotaemia and intestinal malabsorption syndrome. *Journal of Pathology and Bacteriology, 91,* 545–561.

Genant, H. K., Heck, Ll., Lanzl, L. H., Rossman, K., Horst, D. T. R., and Paloyan, E., 1973. Primary hyperparathyroidism. A comprehensive study of clinical, biochemical and radiographic manifestations. *Radiology, 109,* 513–524.

Greenfield, G. B., 1972. Roentgen appearance of bone and soft tissue changes in chronic renal disease. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 116,* 749–757.

Jones, G., 1969. Radiological appearances of disuse osteoporosis. *Clinical Radiology, 20,* 345–353.

Kaye, M., 1964. Mineral analysis of the fourth lumbar vertebra in health and renal failure. *Journal of Clinical Investigation, 43,* 1367–1372.

McLaughlin, M., Raggatt, P. R., Fairney, A., Brown, D. J., Lester, E., and Willis, M. R., 1974. Seasonal variations in serum 25-hydroxycholecalciferol in healthy people. *Lancet, 1,* 536–538.

Meema, H. E., and Meema, S., 1972. Comparison of morphometric findings in the hand bones with densitometric findings in the proximal radius in thyrotoxicosis and in renal osteodystrophy. *Investigative Radiology, 7,* 88–96.

Meema, H. E., Rabinovich, S., Meema, S., Lloyd, G. T. and Orepoulos, D. G., 1972. Improved radiological, diagnosis of azotemic osteodystrophy. *Radiology, 102,* 1–10.

Meema, H. E., and Schatz, D., 1970. Simple radiologic demonstration of cortical bone loss in thyrotoxicosis. *Radiology, 97,* 9–15.

Morgan, D. B., Spiers, F. W., Pulvertaft, C. N., and Fourman, P., 1967. The amount of bone in the metacarpal and the phalanx according to age and sex. *Clinical Radiology, 18,* 101–108.

Platts, M. M., Grech, P., McManners, T., and Cochran, M., 1973. Skeletal changes in patients treated by regular haemodialysis in the Sheffield area. *British Journal of Radiology, 46,* 585–593.

Pugh, D. G., 1951. Subperiosteal resorption of bone: a roentgenological manifestation of primary hyperparathyroidism and renal osteodystrophy. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 66,* 577–586.

Siddiqui, J., and Kerr, D. N. S., 1971. Complications of renal failure and the response to dialysis. *British Medical Bulletin, 27,* 153–159.

Simpson, W., Kerr, D. N. S., Hill, A. V. L., and Siddiqui, J., 1973a. Skeletal changes in patients on regular hemodialysis. *Radiology, 107,* 313–320.

Simpson, W., Young, J. R., and Clarke, F., 1973b. Pseudo-fractures resembling stress fractures in Punjabi immigrants with osteomalacia. *Clinical Radiology, 24,* 83–89.

Steinbach, H. L., Gordan, G. S., Eisenberg, E., Crane, J. T., Silverman, S. and Goldman, L., 1961. Primary hyperparathyroidism. A correlation of roentgen, clinical and pathologic features. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 86,* 329–343.

Steinbach, H. L., and Noetzli, M., 1964. Roentgen appearance of the skeleton in osteomalacia and rickets. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 91,* 955–971.

1976, *British Journal of Radiology*, *49*, 111–117 FEBRUARY 1976

Loss of renal tissue in the elderly

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(Received May, 1975)

ABSTRACT

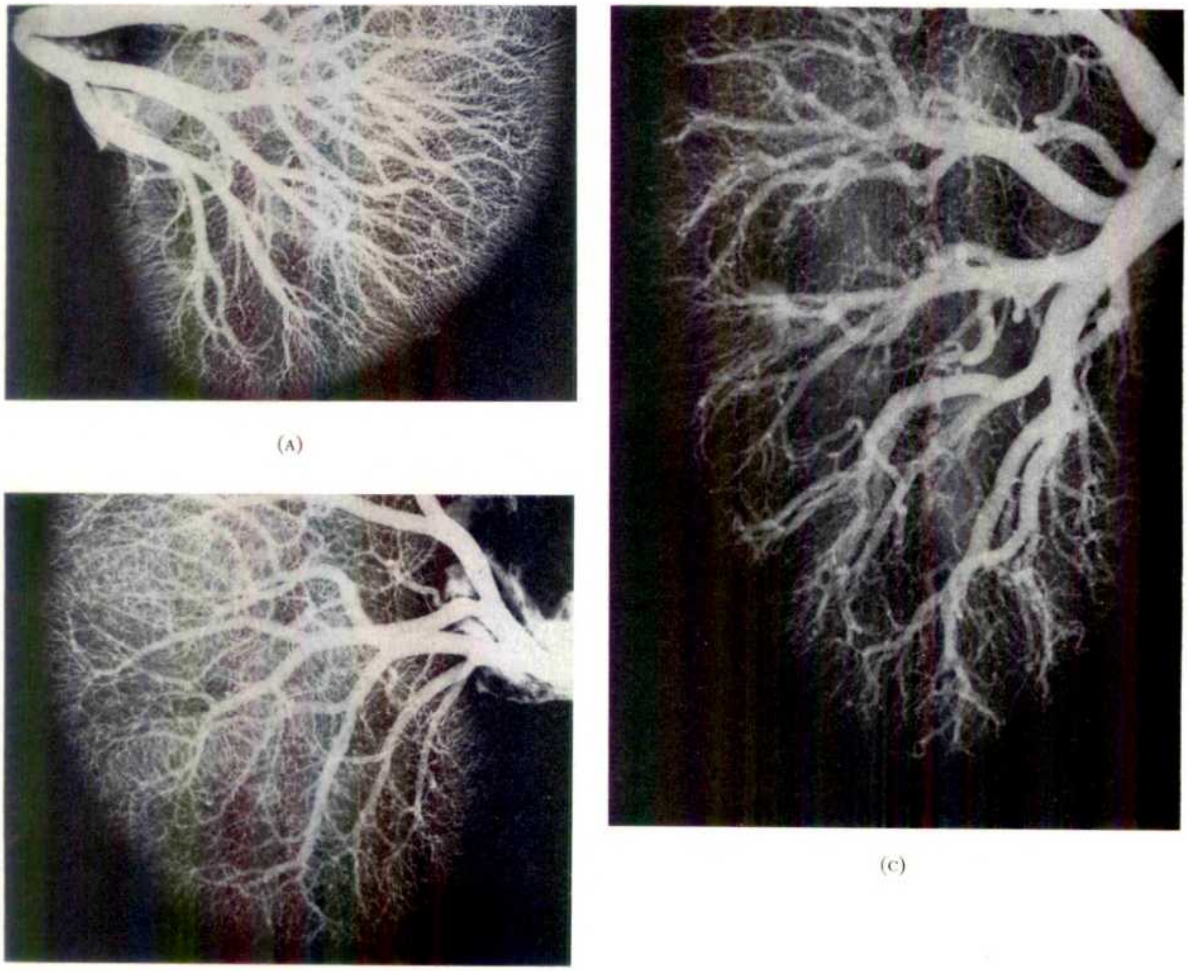
Eighty-eight kidneys obtained at necropsy from normotensive subjects aged over 50 years were examined histologically and by post-mortem pyelography and angiography. Moderate or severe scarring was present in 50 per cent. Its distribution and the absence of calyceal deformity make pyelonephritic scarring unlikely. Its extent was related to the severity of change in the renal vessels, but not to age. On pyelograms, scarring was difficult to distinguish from fetal lobation. Kidneys with the most severe histological changes in the vessels tended to show the most marked angiographic distortion, though in general the two techniques examine different parts of the renal vascular bed. Total renal area and "cortical" area, measured from the angiograms, were not significantly correlated with age, though both tended to be smaller in older subjects. These dimensions, particularly cortical area, were significantly correlated with vascular changes, being smallest when vessels were most markedly affected. Results suggest that the loss of renal tissue which occurs in the elderly, particularly selective loss of cortex, is more closely related to events in the renal vasculature than to age itself.

The human kidney, as it ages, becomes smaller (Roessle and Roulet, 1932; de Leon, Garcia and de Jesus, 1933; Wald, 1937; Dunnill and Halley, 1973). Loss of tissue, which may be focal, in the form of scarring, or diffuse, is believed to result from changes in renal vessels. Until recently this belief has depended almost entirely on histological evidence. Oliver (1952) summarized conventional histological opinion and concluded that if "senescent involution occurs in the kidney of man, it is obscured and its effects [are] over-shadowed by secondary tissue changes that develop as a result of the normal ageing of the renal arteries". Careful morphological and haemodynamic studies in the senescent kidney (Takazakura *et al.*, 1972; Hollenberg *et al.*, 1974) tend to support this view. However, these vascular changes, which, in the absence of hypertension, develop gradually, are invariably not present even in old age (Darmady, Offer and Woodhouse, 1973; Robinson and Herdson, 1973), and little information exists on the extent to which maturation and ageing affect different parts of the human kidney. Commenting on this, Dunnill and Halley (1973) showed a selective loss of cortex and like Moore (1931) a loss of glomeruli in the ageing kidney, but did not relate changes to events in the renal vessels.

In kidneys obtained at necropsy from normotensive subjects aged over 50 years, we have quantified the degree of vascular change assessed histologically and by post-mortem angiography. We have correlated these changes with renal dimensions, including cortical area estimated from angiograms, and with the extent of focal scarring. Since pyelography distinguishes between ischaemic and pyelonephritic scarring more readily than standard morbid anatomical techniques (Hodson, 1959; Kimmelstiel *et al.*, 1961; Smith, 1962; Heptinstall, 1966), we have also examined these kidneys by post-mortem pyelography.

MATERIALS AND METHODS

Eighty-eight kidneys were obtained at routine necropsy in 82 normotensive subjects, aged over 50 years, dying of conditions unrelated to the urinary tract. Though many kidneys were scarred, none had macroscopic or histological evidence of abnormality other than arteriosclerotic nephrosclerosis (see below). Small cortical cysts, which did not distort shape, were present in a few. In 76 subjects one kidney was obtained. This was the right kidney in all except two subjects in which the right was damaged on removal and the left was taken. In six subjects both kidneys were removed. Fifty-five subjects were male (mean age 68 years; range 51–90 years), 27 female (mean age 68 years; range 52–88 years). Kidneys were removed with their vascular pedicles and a length of ureter. Perirenal fat was carefully removed, leaving capsule and capsular vessels intact. The origin of the renal artery was examined in all subjects and no significant narrowing observed. Retrograde pyelography and renal arteriography were performed within 24 hours of necropsy. Pyelography was performed first. Hypaque 45 per cent (Winthrop) was injected by hand through a catheter ligated into the ureter. Four radiographs were obtained using non-screen film (Osray M3) at a focus-film distance of 100 cm. Focal spot size was 0·8 mm. Kidneys were placed directly on the film envelope. Antero-posterior and lateral radiographs were obtained, together with two oblique views for which the kidneys were rotated 45 deg. in each direction about their long axis. The contrast medium was washed from the pelvicalyceal system and the catheter removed. A catheter was then inserted into the renal artery and ligated into position. The renal vein was tied.



(A)

(B)

(C)

FIG. 1.

Post-mortem renal angiograms in different subjects showing various grades of vascular change.

(A) Left kidney. Slight tortuosity of arcuate and interlobular arteries. Angiographic score for whole kidney = 9 out of 30.

(B) Right kidney. Moderately tortuous arcuate and interlobular arteries. Angiographic score = 15 out of 30.

(C) Right kidney. Interlobar, arcuate and interlobular arteries are tortuous and irregular. Marked underfilling of fine peripheral vessels. Angiographic score = 30 out of 30.

Undiluted colloidal barium (Micropaque, Damancy) which had been strained through gauze, was injected by hand. Filling was judged to be satisfactory when barium appeared in peripheral cortical vessels producing a speckled white appearance on the renal surface. The catheter was removed and the artery ligated. Radiographs were obtained in four positions as before using fine-grain industrial film (Structurix D4). All films were developed by hand.

The pyelograms were examined for evidence of deformity of calyces or renal outline. Scarring was defined as localized loss of renal substance, usually resulting in indentation of renal outline, visible on antero-posterior or oblique radiographs. The distribution of scarring was recorded. Indentations visible only on lateral radiographs or considered to be due to fetal lobation were recorded separately. Lobation was defined as single or multiple indentations, usually more smoothly contoured than scarring, lying between groups of calyces. Vascular appearances were judged from the angiograms (Fig. 1). Vessels were assessed for tortuosity and variation in calibre at each of three sites: the mid portion and the poles. Interlobar, arcuate and interlobular arteries were assessed separately. Each of these three groups of vessels in the three sites was graded numerically on a four-point scale from 0 to 3, grade 3 representing the most severe degree of change. Thus each site had a maximum possible score of 9, the total for all three sites being 27. In addition, the extent of underfilling of small vessels was assessed for the whole kidney on a scale of 0–3, grade 3 representing the most severe underfilling. This brought the final maximum possible score for the most severely affected kidney to 30. Post-mortem angiograms obtained in ten histologically normal kidneys from subjects aged 19–45 years, dying as a result of trauma or of diseases unrelated to the kidney, were used as reference standards. All radiographs were assessed by two radiologists (G.J.G. and M.S.F.M.). Total renal area and "cortical" area, which ignored the renal columns and was defined as the area peripheral to the arcuate arteries, were measured from antero-posterior angiograms. The renal outline and the line formed by the arcuate arteries were traced on to cardboard. When arcuate arteries close to the hilum could not be clearly defined, the line formed by the arcuate arteries was continued parallel to the hilar concavity. The areas of the whole kidney and its cortex were cut out and weighed separately and together. These were then compared with a standard of known area.

The kidneys were then examined by a pathologist (K.B.R.). The surface of the kidney was inspected and the extent of any scarring graded as mild, moderate or severe. Mild scarring occupied up to 10 per cent of renal surface area, moderate scarring occupied 10–50 per cent, and severe scarring over 50 per cent. Kidneys were cut longitudinally and the macroscopic appearances of the pelvicalyceal system were noted. Tissue blocks were obtained routinely from the apical, anterior and posterior segments. Additional blocks were obtained from areas noted to be abnormal. The tissue blocks were placed in 10 per cent buffered formol saline and all blocks processed for light microscopy. 5μ sections stained by haematoxylin and eosin were examined. Where indicated 2μ sections were stained for basement membrane, connective tissue, elastin and fibrin. Histological assessment was made without knowledge of the results of clinical, laboratory or radiological investigations. Pathological criteria were those of Heptinstall (1966). These have recently been summarized by one of us (Robinson and Herdson, 1973). In arteriosclerotic nephrosclerosis, interlobar and arcuate arteries showed intimal fibrosis, interlobular arteries showed fibro-elastic intimal thickening and arterioles showed irregular hyaline disease. Change was more marked in arteries than arterioles. This condition, which is usually but not invariably present in the senescent kidney (Robinson and Herdson, 1973), was categorized as mild, moderate or severe. Kidneys with evidence of benign or malignant hypertensive nephrosclerosis were not included in the study.

RESULTS

Indentations of the renal outline

On antero-posterior and oblique radiographs, 40 of the 88 kidneys were considered to be scarred. Direct inspection showed moderate or severe scarring in 35 of these, no scars in one and fetal lobation alone in four. In a further nine, direct inspection revealed moderate or severe scarring, not visible on antero-posterior and oblique radiographs. Thus, 44 kidneys (50 per cent) were at least moderately scarred on direct examination; 11 (12·5 per cent) were severely scarred. No age or sex differences were observed. The midportion of the kidney was affected as frequently as the poles. Scars were common on the anterior and posterior surfaces, usually extending from other sites, though in six kidneys they were visible only on a lateral radiograph. Shallow flat scars occurred as frequently as deep "V"-shaped scars. No kidney showed calyceal deformity, either on pyelography or direct inspection.

Radiologically, 12 kidneys were thought to show fetal lobation. Direct inspection confirmed this in only four. In the other eight, fine granularity of the renal surface produced a slightly uneven renal outline which conformed to our radiological definition of lobation (Fig. 2). In another four kidneys, referred to above, lobation was mistaken for scarring at pyelography.

Renal dimensions

Mean total renal area was 55·2 cm^2 (range 30·0–72·6 cm^2). Mean cortical area was 12·7 cm^2 (range 6·7–20·4 cm^2). Neither was significantly correlated with age but, in subjects over 65 years old, both renal area ($p < 0{\cdot}05$) and cortical area ($p < 0{\cdot}01$) were smaller. Both were smaller in females ($p < 0{\cdot}01$–$0{\cdot}001$). Cortical area comprised, on average, 23 per cent of total renal area (range 12–34 per cent). This fraction was slightly, but not significantly, less in subjects over 65 ($0{\cdot}05 < p < 0{\cdot}1$); no sex difference was observed.

Vascular appearances

Mean angiographic score was 19 out of 30 (range

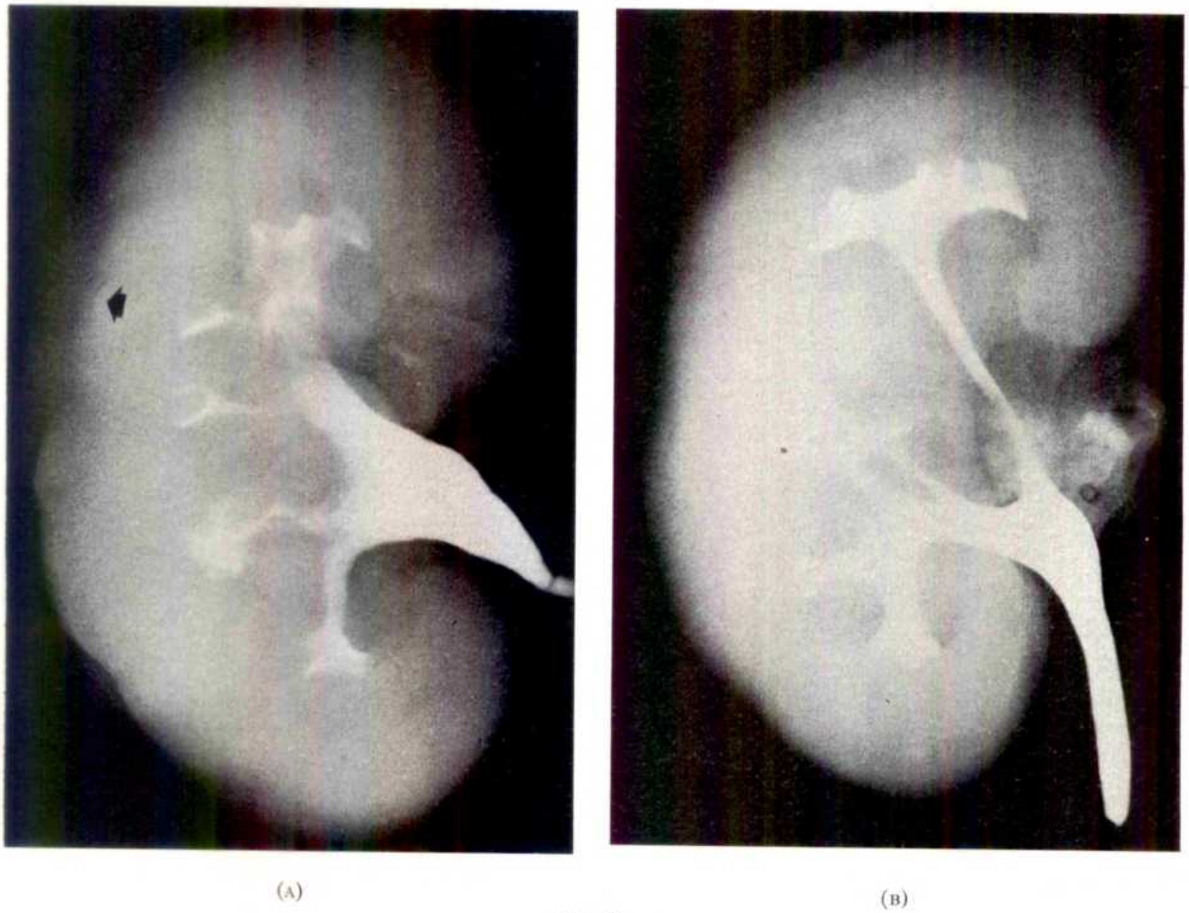

(A) (B)

FIG. 2.

Post-mortem pyelograms of kidneys showing similarity between fetal lobation (A) and diffuse granular scarring (B). The deep indentation (arrowed in A) was incorrectly considered to be a flat scar. The slight indentations due to scarring in (B) do not, in general, overlie calyces and were thought to be due to mild lobation.

1–30). Scores were higher for interlobular arteries than for arcuate arteries ($p < 0{\cdot}001$); arcuate arteries had higher scores than interlobar arteries ($p < 0{\cdot}001$). Scores were higher at the poles than in the midportion ($p < 0{\cdot}02$–$0{\cdot}01$) but upper and lower poles did not differ significantly. Scores in severely scarred kidneys were higher than scores in kidneys which were moderately ($p < 0{\cdot}01$) or mildly ($p < 0{\cdot}001$) scarred. No significant correlation existed between angiographic score and age. No sex difference was observed. A negative correlation existed between angiographic score and total renal area ($r = -0{\cdot}35$, $p < 0{\cdot}001$). A better negative correlation (Fig. 3) existed between score and cortical area ($r = -0{\cdot}48$, $p < 0{\cdot}001$). This was improved slightly ($r = -0{\cdot}52$, $p < 0{\cdot}001$) by the exclusion of kidneys showing moderate or severe scarring.

Angiographic scores in kidneys showing severe histological change were higher than scores in those in which changes were moderate ($p < 0{\cdot}01$) or mild ($p < 0{\cdot}001$). Mean age, in years, of subjects showing mild histological change (66·4; SEM 1·3) was slightly less than mean age of subjects with moderate (68·7; SEM 1·3) or severe (72·7; SEM 3·2) changes. Differences are not significant. Kidneys with mild histological change were less extensively scarred than those with moderate ($p < 0{\cdot}05$) or severe ($p < 0{\cdot}001$) changes. Cortical thickness diminished as histological change became more severe (Fig. 4).

DISCUSSION

The histological distinction between pyelonephritic and ischaemic renal scarring is often difficult. Glomerular sclerosis, tubular atrophy and interstitial

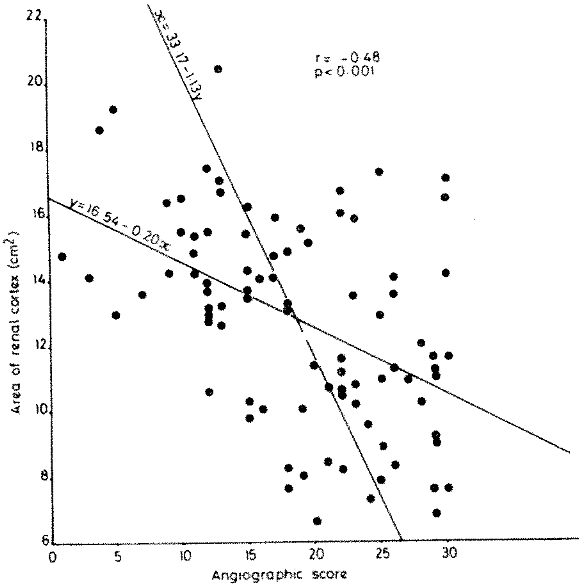


FIG. 3.
Correlation between renal cortical area and angiographic score.

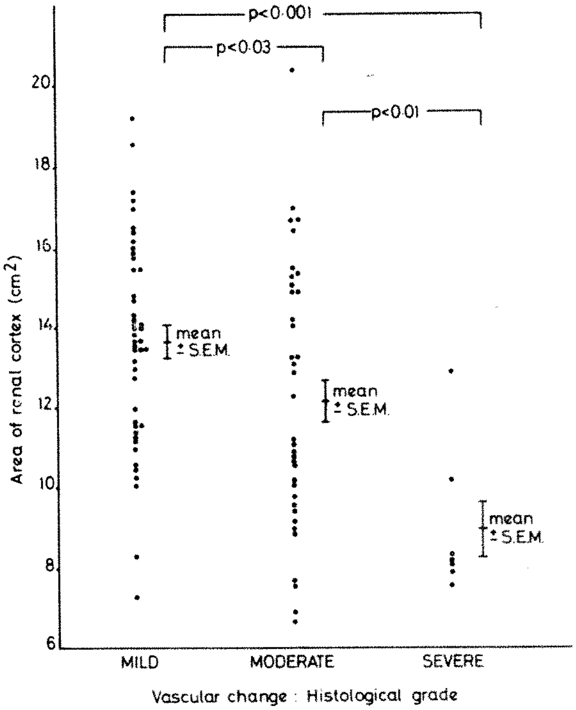


FIG. 4.
Renal cortical area and degree of vascular change, assessed histologically.

changes occur in both arteriosclerotic nephrosclerosis and chronic pyelonephritis (Heptinstall, 1966). In the present study, a histological diagnosis of arteriosclerotic nephrosclerosis was made only if, in addition to these appearances, the interstitial inflammatory infiltrate was predominately lymphocytic. According to Kimmelstiel *et al.* (1961), an active pleomorphic inflammatory infiltrate, particularly accumulation of polymorphs, provides the most reliable histological evidence of chronic pyelonephritis. Like them, we found macroscopic assessment of the contour of scars to be unhelpful. Radiologically the papillary distortion which is characteristic of pyelonephritic scarring manifests itself as calyceal clubbing (Hodson, 1959). Smith (1962), examining scarred kidneys removed at surgery or necropsy, emphasized both the importance of careful naked eye inspection of calyces and the anatomical difficulty involved. He made only limited use of pyelography, which is easily performed and provides a permanent record of appearances. Post-mortem pyelography demonstrated calyceal deformity in none of the 88 kidneys in the present series, an observation confirmed by direct inspection. However, scarring was common. In our view, it would have been visible as localized indentations of the outline of 35 kidneys (40 per cent) during the nephrogram phase at intravenous urography. In 12·5 per cent of kidneys scarring was severe, a figure in accord with the observations of Howell and Piggot (1948) and McKeown (1965) in kidneys from elderly subjects. Scars occurred at all sites in the kidney, unlike pyelonephritic scars, which are usually polar (Hodson, 1968). Indeed scarring frequently occurred on the anterior or posterior surfaces of the kidney. Partly as a result we failed radiologically to recognize indentation of the renal outline in nine kidneys (10 per cent), despite oblique views. We wrongly diagnosed fetal lobation in eight kidneys in which granularity of the surface of the kidneys produced slight undulation of its outline; in another four we mistook lobation for scarring. Nonetheless we regard post-mortem pyelography as a valuable examination when calyceal deformity is suspected. Considered with the macroscopic and histological evidence it has allowed us to conclude that the scarring which we observed was not pyelonephritic.

It is likely that the scars were ischaemic. Vascular changes tended to be most marked in the most extensively-scarred kidneys. Histologically, 49 per cent of kidneys showed moderate or severe change and 44 per cent had an angiographic score greater than 20 out of 30. The two techniques are complementary, in general examining different parts of the renal vascular bed. Though we found significantly higher angiographic scores in kidneys with histological evidence of severe vascular change, small peripheral vessels may be affected independently of events in larger arteries. Downs (1970), in kidneys removed from normotensive subjects, noted angiographic abnormality of interlobar and arcuate arteries when cortical arterioles were histologically normal. With others (Bell, 1950; Oliver, 1952), we found histological change to be more pronounced in arteries than arterioles. Angiographically, however, we observed the most severe change in the most peripheral arteries, particularly those at the poles, although scarring was no more common there. Davidson, Talner and Downs (1969) made similar conclusions. Like them, we found no correlation between severity of vascular change and age in subjects over 50 years old, observations which resemble those of Ljungqvist and Lagergren (1962) in afferent arterioles. This is not to deny that significant differences in angiographic appearances exist when young and elderly normotensive subjects are compared, both in specimens (Davidson *et al.*, 1969) and in life (Hollenberg *et al.*, 1969).

Even in the absence of localized scarring, the size of the human kidney begins to diminish at about 50 years of age (Roessle and Roulet, 1932; De Leon *et al.*, 1933; Wald, 1937, Dunnill and Halley, 1973). Though this, together with an age-related decline in renal function (Lewis and Alving, 1938; Davies and Shock, 1950), has been documented for many years, Dunnill and Halley, in 1973, found "surprisingly little" information in the literature about the quantitative anatomy of the normal human kidney at various ages. Studying tissue loss from different parts of the kidney by point counting techniques, they noted a marked reduction in the volume of the cortex, beginning in middle age, and confirmed earlier work (Moore, 1931) which demonstrated a fall in the number of glomeruli. Changes in the renal vessels are also well described (Bell, 1950; Oliver, 1952; McKeown, 1965) but differences in definition have led to difficulties in quantifying these and in comparing the results of published series (Darmady *et al.*, 1973). Only recently have attempts been made to relate renal vascular changes directly to loss of renal substance (Takazakura *et al.*, 1972; Hollenberg *et al.*, 1974). Renal area, measured from radiographs, is well correlated with renal weight, despite a small increase in the amount of fat in the renal sinus, as the kidney ages (Moell, 1961; Griffiths, Cartwright and McLachlan, 1975). In the present study, cortical area and total renal area tended to be smaller in older subjects but no significant correlation existed between either of these measurements and age. The relationship between renal dimensions and vascular change, judged either histologically or angiographically, was better. In particular, we observed a highly significant correlation between angiographic score and cortical area, a correlation which persisted when kidneys showing marked localized loss of tissue in the form of scarring were excluded. We regard this as further evidence that the decline in renal size which occurs with ageing, particularly diffuse loss of cortical tissue, is more closely related to changes in renal vasculature than to age itself.

ACKNOWLEDGEMENTS

We are grateful to Mr. Robert Newcombe, Department of Medical Statistics, Welsh National School of Medicine, for his help and advice. Mr. E. E. Roberts rendered valuable technical assistance. The Department of Medical Illustration Welsh National School of Medicine, prepared the illustrations.

REFERENCES

BELL, E. T., 1950. In *Renal Diseases*, pp. 331–346 (Lea and Febiger, Philadelphia).

DARMADY, E. M., OFFER, J., and WOODHOUSE, M. A., 1973. The parameters of the ageing kidney. *Journal of Pathology*, *109*, 195–207.

DAVIDSON, A. J., TALNER, L. B., and DOWNS, W. M., 1969. A study of the angiographic appearance of the kidney in an ageing normotensive population. *Radiology*, *92*, 975–983.

DAVIES, D. F., and SHOCK, N. W., 1950. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *Journal of Clinical Investigation*, *29*, 496–507.

DE LEON, W., GARCIA, A., and DE JESUS, P. I., 1933. Normal weights of visceral organs in adult Filipinos. *Philippine Journal of Science*, *52*, 112–118.

DOWNS, W. M., 1970. A study of the angiographic appearance of the kidney in an ageing normotensive population. M. D. Thesis, Yale University School of Medicine. Quoted by Davidson, A. J. and Talner, L. B. (1973). Lack of specifity of renal angiography in the diagnosis of renal paenchymal disease. *Investigative Radiology*, *8*, 90–95.

DUNNILL, M. S., and HALLEY, W., 1973. Some observations on the quantitative anatomy of the kidney. *Journal of Pathology*, *110*, 113–121.

GRIFFITHS, G. J., CARTWRIGHT, G. and MCLACHLIN, M. S. F., 1975. Estimation of renal size from radiograph; is the effort worthwhile? *Clinical Radiology*, *26*, 249–256.

HEPTINSTALL, R. H., 1966. In *Pathology in the Kidney*, pp. 421–454. (Churchill, London).

HODSON, C. J., 1959. Radiological diagnosis of pyelonephritis. *Proceedings of the Royal Society of Medicine*, *52*, 669–672.

1968. Radiological diagnosis of renal involvement. In *Urinary Tract Infection*, ed. F. O'Grady, and W. Brumfitt, pp. 108–112 (Oxford University Press).

HOLLENBERG, N. K., EPSTEIN, M., BASCH, R. I., and MERRILL, J. P., 1969. "No man's land" of the renal vasculature. An arteriographic and haemodynamic assessment of the interlobar and arcuate arteries in essential and accelerated hypertension. *American Journal of Medicine*, *47*, 845–854.

HOLLENBERG, N. K., ADAMS, D. F., SOLOMON, H. S., RASHID, A., ABRAMS, H. L., and MERRILL, J. P., 1974. Senescence and the renal vasculature in normal man. *Circulation Research*, *34*, 309–316.

HOWELL, T. H. and PIGGOT, A. P., 1948. The kidney in old age. *Journal of Gerontology, 3*, 124–128.

KIMMELSTIEL, P., KIM, O. J., BERES, J. A., and WELLMAN, K., 1961. Chronic pyelonephritis. *American Journal of Medicine, 30*, 589–607.

LEWIS, W. H., and ALVING, A. S., 1938. Changes with age in the renal function in adult men. *American Journal of Physiology, 123*, 500–515.

LJUNGQVIST, A., and LAGERGREN, C., 1962. Normal intrarenal arterial pattern in adult and ageing human kidney. A microangiographic and histological study. *Journal of Anatomy, London, 96*, 285–300.

MCKEOWN, F., 1965. In *Pathology of the Aged*, pp. 171–204. (Butterworths, London).

MOELL, H., 1961. Kidney size and its deviation from normal in acute renal failure. *Acta Radiologica, Supplement, 206*, 1–74.

MOORE, R. A., 1931. The total number of glomeruli in the normal human kidney. *Anatomical Record, 48*, 153–168.

OLIVER, J., 1952. In *Cowdry's Problems of Ageing*, ed. A. I. Lansing, pp. 631–650 (Williams and Wilkins, Baltimore).

ROBINSON, K. B., and HERDSON, P. B., 1973. The incidence of kidney disease in two hundred necropsies. *New Zealand Medical Journal, 78*, 517–519.

ROESSLE, R., and ROULET, F., 1932. In *Mass und Zahl in der Pathologie*, pp. 63–66 (Springer-Verlag).

SMITH, J. F., 1962. The diagnosis of the scars of chronic pyelonephritis. *Journal of Clinical Pathology, 15*, 522–526.

TAKAZAKURA, E., SAWABU, N., HANDA, A., TAKADA, A., SHINODA, A., and TAKEUCHI, J., 1972. Intrarenal vascular changes with age and disease. *Kidney International, 2*, 224–230.

WALD, H., 1937. The weight of normal adult human kidneys and its variability. *Archives of Pathology, 23*, 493–500.

Book review

Differential Diagnosis of Gastric Diseases. By Keiichi Kawai and Hiromichi Tanaka, pp. 162 (110 illus.), 1974 (Tokyo, Igaku Shoin Ltd., Berlin, Heidelberg, New York, Springer-Verlag), $68.60.

The expertise which Japanese doctors have brought to bear on the radiology and endoscopy of the stomach has become increasingly appreciated during the past ten years. The two techniques are complementary and possess specific advantages and disadvantages of their own. It is not rare in Japan that one doctor uses both radiology and endoscopic techniques since they have found that mastery and skill in the use of these two diagnostic techniques together greatly enhances the possibilities of correct diagnosis. The two authors of this book are experts in both fields.

The book is divided into two main sections. The first concerns the fundamentals of radiological techniques, including a general description of their methods with technical detail of the methods of examinations. They stress the need for making use of all the available radiological evidence, including mucosal pattern, the outline when the stomach is filled with barium and the appearance when the stomach is fully distended and double contrast is employed. Finally, the importance of compression views made with varying degrees of compression is emphasized. To make use of only one type of technique is to miss valuable information. They make no reference to the use of relaxants such as Buscopan (Hyoscine-N-butylbromide) and give no details of the type of barium preparation they consider best.

They go into similar details of the fundamentals of endoscopic diagnosis including many practical suggestions for overcoming difficulties and limitations inherent in this technique. They describe in detail the way in which biopsies should be taken from suspected areas in the stomach.

The main section of the book consists of a number of case presentations of different types of pathological lesions divided into those which are predominantly the protruding type, and those which are the excavating type. In each section there are descriptions of clinical cases in which the radiology is correlated with the endoscopic findings and the pathological diagnosis. The radiological reproductions are in the negative, that is barium appears black. These are usually accompanied by coloured photographs of the appearances of the lesion at endoscopy and a photograph of the pathological specimen and histological sections. They describe a number of cases which they consider to be typical and others in which the features do not allow a definitive diagnosis to be made. They also include a section on rare cases for as they say "it is important to know of cases diagnosed by other doctors besides the limited cases of one's own experience. Medicine is experimental diagnostics and an excellent physician has the features of rare and difficult cases classified in an orderly manner in his mind".

The language is sometimes rather stilted, and there are some minor typographical errors which do not detract from the value of the book which will be of great interest to all engaged in gastro-intestinal radiology. It emphasizes the need for close co-operation between the radiologists and endoscopists who are using complementary techniques in order to arrive at a more complete diagnosis for the benefit of the patient.

J. W. LAWS.

1976, *British Journal of Radiology*, *49*, 118–122

Levels of ioglycamate (Biligram) in the bile of the rhesus monkey following intravenous infusion at different dose-rates

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(*Received March, 1975*)

ABSTRACT

The maximum rate of excretion of ioglycamate in the bile of the rhesus monkey was achieved when the rate of administration was at least twice the rate of excretion. A maximum concentration of ioglycamate in the bile was also established, and this is more important to the visualization of the bile-ducts than the quantity of ioglycamate excreted. The maximum concentration was obtained at the same rate of infusion as that which produced the maximum rate of excretion. The peak concentration was sustained longer with an infusion lasting two hours than with one lasting 36 minutes, although the same quantity of ioglycamate had been administered.

It is concluded that an infusion at a rate equal to twice the maximum excretory rate and continued for two hours or longer is a rational approach to intravenous cholangiography particularly in those patients where there has been some difficulty in bile-duct visualization.

There is still conflict in the literature as to the relative merits of performing intravenous cholangiography by an infusion technique instead of the more widely used single bolus injection. The improvement in bile-duct visualization with the infusion technique reported by some authors (Allen 1969; Feldman and Keohane, 1966; McNulty 1968; Payne, 1968), has not been found by others (Darnborough and Geffen, 1966; Foy, 1968; Margolin and Obata, 1968). However, most authors agree that toxic side effects are fewer with the infusion technique, and there is evidence that the concentration of iodipamide in the bile is higher following an infusion than following a bolus injection (Whitney and Bell, 1972).

We have measured the excretion of ioglycamate in the bile of the rhesus monkey following different rates of infusion, and following infusions of different duration, in order to determine a rational approach to intravenous cholangiography. The monkey model used enabled the excretion and concentration of ioglycamate in the bile to be measured while maintaining an "intact" entero-hepatic circulation of bile acids. The importance of maintaining an intact entero-hepatic circulation when investigating the excretion of biliary contrast agents has been previously stressed (Whitney and Campbell, 1972).

MATERIALS AND METHODS

Experimental animals

The experimental model has been fully described elsewhere (Dowling *et al.*, 1968). Female rhesus monkeys weighing approximately 5 kg were used. The animals had a T-tube tied in the common bile-duct in such a position that the cannula collected both hepatic and gall-bladder bile. The common bile-duct was occluded so that all the bile was collected by the cannula. The bile was passed through an electronic stream splitter to divert one drop in 20 for analysis, and the remaining bile was returned by a second T-tube inserted into the gastric antrum. Both cannulae were exteriorized through separate stab wounds. The monkeys were kept in restraining chairs and were not used for experiments until bile volume and bile salt secretion reached a steady state; this usually took at least two weeks from the time of operation.

Experimental technique

Group A (*four experiments*). Ioglycamate was given by intravenous infusion using a constant infusion pump starting at a rate of 10·5 mg/minute. At 120 minutes from the start of the infusion the rate was increased to 26 mg/minute and this was continued for a further 80 minutes and the rate was then increased further to 45 mg/minute for 30 minutes. Bile samples were collected from the start of the infusion and continued for 260 minutes.

Group B (*eight pairs of Experiments*). The monkey was given an intravenous infusion for two hours at a rate of 26 mg/minute and the bile samples collected for a total of 180 minutes from the start of the infusion. Two days later the same monkey was given a fast infusion at a rate of about 81 mg/minute lasting for only 36 minutes so that the same quantity of ioglycamate was given, and the bile samples collected as before for 180 minutes. A total of eight pairs of experiments was performed. In two experiments, three blood samples were taken during the course of the infusion, and the plasma concentration of ioglycamate estimated.

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Collection of samples. The T-tube in the common bile-duct was disconnected from the stream splitter and all the bile collected for a ten-minute period. The bile volume was noted, 0·2 ml. was removed for ioglycamate estimation and the remainder then passed through the stream splitter. The enterohepatic circulation of bile salts was therefore only interrupted for a maximum of ten minutes.

Chemicals and estimations

Ioglycamate methylglucamine (17 g in 100 ml.) labelled with a tracer amount of ^{125}I was used. The concentration of ioglycamate in the bile was estimated using a well-type scintillation counter, and the calculations were made by comparing the activity of the sample with the activity of a stock solution. The quantity excreted was calculated from the concentration and the bile volume.

Statistic. The mean and standard error was calculated in Groups A and B. Paired T-testing was used to compare the transport maximum and concentration maximum in Group B.

RESULTS

Group A

The excretion of ioglycamate in the bile following three different rates of intravenous infusion is shown in Fig. 1. The infusion was started at a rate of 10·5 mg/minute and continued at this rate for 120 minutes. No ioglycamate was detectable in the bile in the first twenty minutes from the start of the infusion and the excretion rate rose rapidly from the 30 minute bile sample to reach a level of 7·3 mg/minute by 70 minutes from the start of the infusion. At this stage the excretion rate was 29 per cent less than the rate of administration. The infusion rate was increased to 26 mg/minute and the excretion increased to 12 mg/minute; this was the maximum excretory rate (transport maximum) since a further increase in the infusion rate to 40·5 mg/minute did not increase the rate of excretion. A small depression in the excretion rate occurred following the highest rate of infusion.

The graph of the concentration of ioglycamate in the bile at the different infusion rates (Fig. 2.) was similar to the pattern of excretion. At an infusion rate of 10·5 mg/minute the concentration of ioglycamate in the bile was less than the maximum (37 mg/ml.) which followed the infusion at 26 mg/minute. A further increase in the infusion rate to 40·5 mg/minute did not increase the concentration in the bile.

Group B

The effect of administering the same total of ioglycamate in either 36 minutes or in two hours is shown in Fig. 3. The faster rate of infusion produced the same maximum concentration in the bile as the slower rate but the concentration maximum was reached sooner with the faster rate than with the slower rate of infusion. The concentration remained

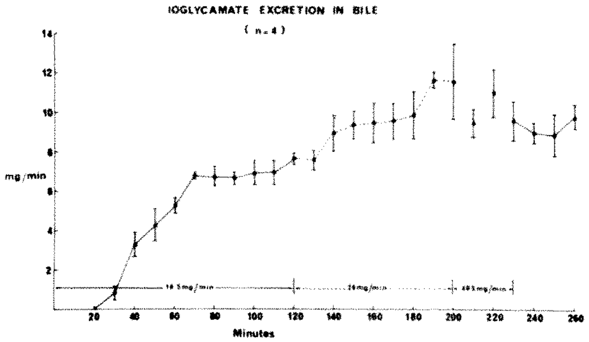

FIG. 1.

The effect of three different rates of infusion on the excretion of ioglycamate in the bile. The infusion was started at a rate of 10·5 mg/minute. No ioglycamate appeared in the bile until 30 minutes from the start of the infusion. The excretion reached a maximum rate of 7·3 mg/minute but increased to 12 mg/minute when the infusion rate was increased to 26 mg/minute. A further increase in the infusion rate to 40·5 mg/minute produced a small depression in the rate of excretion. Each point is the mean of four experiments and the standard error is plotted.

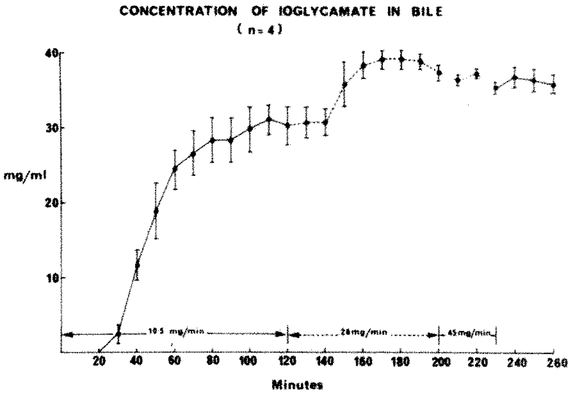

FIG. 2.

The effect of three different rates of infusion on the concentration of ioglycamate in the bile. The infusion was started at a rate of 10·5 mg/minute. The concentration of ioglycamate in the bile rose rapidly and levelled out at 29 mg/minute The concentration increased to 37 mg/ml. when the infusion rate was increased to 26 mg/minute and no further increase in the concentration was produced by increasing the infusion rate to 40·5 mg/minute.

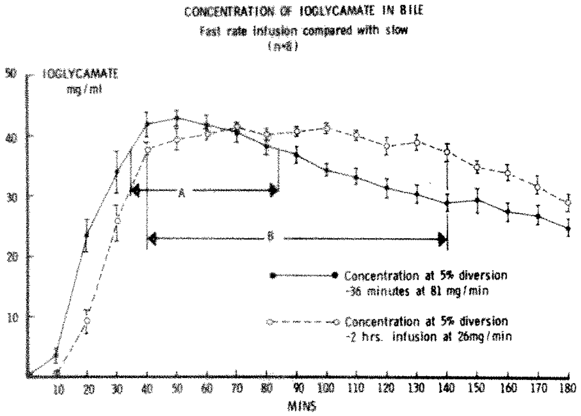

Fig. 3.

The effect of administering the same total quantity of ioglycamate in either 36 minutes or 120 minutes. The faster rate of infusion produced the same maximum concentration as the slower rate but reached it within 35 minutes from the start of the infusion as compared with 70 minutes following the slower rate of infusion, However, the duration of the "peak concentration" was much longer (B) following the longer duration slower infusion than following the faster infusion (A). Each point on the graph is the mean of eight experiments.

within 10 per cent of the maximum for a much longer period following the two-hour infusion than following the 36-minute infusion at the faster rate.

The results have been analysed by paired T-testing to reduce effect of inter-animal variation and the results are shown in Fig. 4. There was no difference in the maximum excretion or the maximum concentration between short or long duration infusion. The duration of the peak concentration was 90 minutes following the two-hour infusion as compared with only 50 minutes following the infusion which lasted only 36 minutes.

The plasma concentration of ioglycamate rose faster when the contrast was given at a faster infusion rate and the results of the two experiments in which the plasma level was estimated are shown in Fig. 5.

Discussion

There appears to be a maximum rate of biliary excretion of organic anions by the liver, and most of these share the same transport mechanism (Sperber and Sperber, 1971). The biliary contrast agents iodipamide and ioglycamate are organic anions and have a maximum rate of excretion, and this rate varies with different species. A value of 7 mg/minute had been found for the excretion of iodipamide in the Boxer dog (Burgener *et al.*, 1970), and the present experiments showed a value of 14 mg/minute for the excretion of ioglycamate in the rhesus monkey. A rate of administration equal to the maximum excretory rate is all that is required to sustain the transport maximum of a substance such a bromsulphthalein which is almost entirely excreted via the liver (Wheeler, Meltzer and Bradley, 1960), but an infusion rate of 26 mg/minute, nearly twice the maximum excretory rate, was required to sustain the transport maximum for ioglycamate. A similar finding has been reported for the excretion of ioglycamate in the rat, where an infusion rate of twice the excretory rate was necessary (Sperber and Sperber, 1971).

Following injection of the contrast agent there is a rapid fall in its concentration in the plasma due to the distribution in extracellular water, although, unlike bromsulphthalein there is no hepatic storage of either iodipamide or ioglycamate (Sperber and Sperber, 1971). The distribution in the extracellular water may in part account for the high

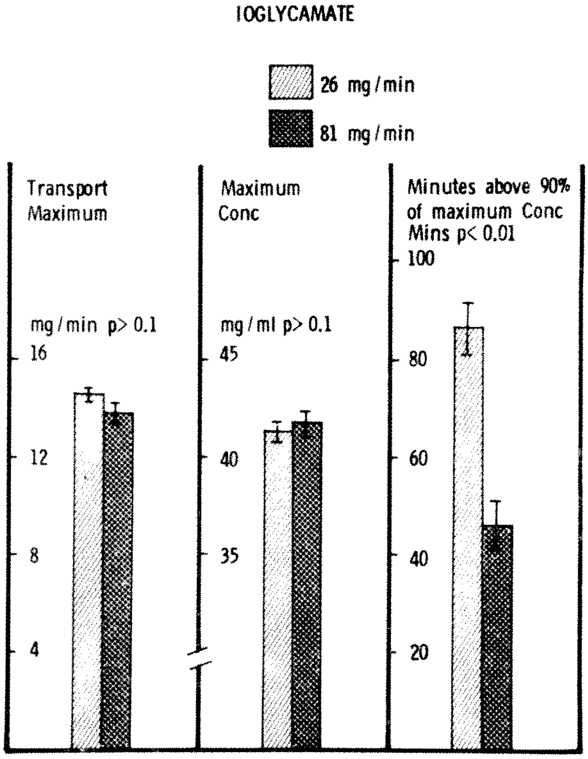

Fig. 4.

The results shown in Fig. 3 have been analysed by paired T-testing in order to reduce the effect of inter-animal variability and the results are shown in this histogram. There was no difference in the maximum concentration or maximum excretion rate following the two different rates of infusion. The duration of the "peak concentration" was considerably longer with the slower, longer duration infusion.

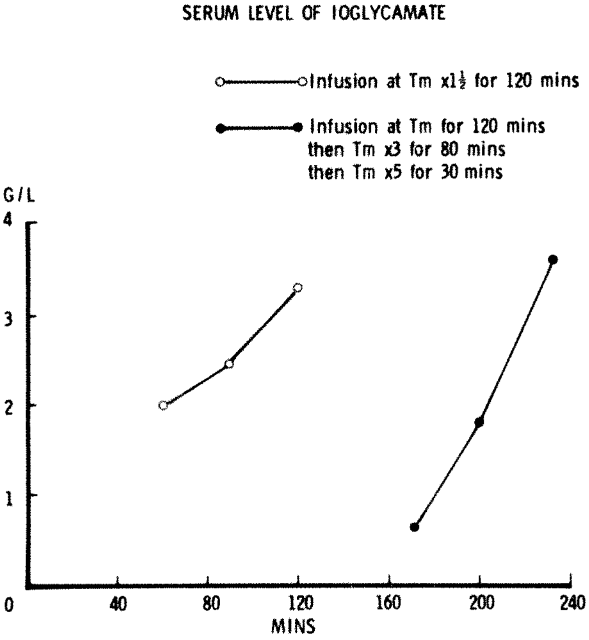

Fig. 5.

The results of measuring plasma concentration of ioglycamate at different rates of intravenous infusion. The open circles show the plasma concentration when the infusion rate was one and a half times the Tm. The closed circles show the plasma concentration achieved in a second experiment in which the infusion rate was the same as the transport maximum for 120 minutes and then the infusion rate was increased to three times and then to five times the Tm. The time in minutes is from the start of the infusion. The plasma concentration of ioglycamate rose rapidly with the fast infusion rates.

infusion rate necessary to maintain the maximum biliary excretion, and would make it impossible to use the indirect technique (Wheeler *et al.*, 1960) to assess the transport maximum from changes in plasma concentration. Furthermore, between 10 per cent and 29 per cent of the administered dose of ioglycamate is excreted in the urine (Taenzer and Herms, 1971), and in the present experiments only seventy per cent of the administered dose was excreted in the bile when the rate of infusion was below the transport maximum. An infusion rate of three times the rate of excretion depressed the excretion of ioglycamate. This phenomenon is well established for systems with a maximum transfer rate and occurs with iodipamide in the dog and the rat (Cook *et al.*, 1952; Fischer, 1965; Sperber and Sperber, 1971). It has been suggested that the depression of iodipamide excretion at high rate of administration does not occur with ioglycamate (Sperber and Sperber, 1971), but the present experiments do not confirm that finding.

To decide upon the optimum rate of intravenous infusion in man requires knowledge of the maximum biliary excretory rate. A value of 30 mg/minute in non-jaundiced patients has been suggested, and successful cholangiograms have been obtained using an infusion rate of 50 mg/minute (Miller *et al.*, 1969). These values were obtained from patients with T-tubes in the bile-duct, and may be inaccurate since bile volume and composition do not return to normal for at least two weeks following surgery on the biliary tree, with the measurements usually having to be carried out within this period (Dowling, Mack and Small, 1970). Furthermore, this value would not apply to patients with liver disease or jaundice, where the excretion of ioglycamate would be expected to be depressed in a similar manner to the excretion of bromsulphthalein.

The concentration of ioglycamate in the bile at different rates of infusion followed a similar pattern to the excretion (Fig. 2). The maximum concentration was not reached until the infusion rate was sufficient to produce the maximum rate of excretion, and even a further increase in the rate of administration did not increase the concentration in the bile. There was therefore a concentration maximum as well as a transport maximum and this would be expected since bile remains virtually isosmotic with plasma (Sperber and Sperber, 1971). Any increase in the excretion of ioglycamate by the hepatocyte would be accompanied by an incremental increase in the bile volume. It is the concentration of ioglycamate in the bile and not the quantity excreted which determines radiographic density, and a concentration of iodine of 10 mg/ml. is required for visualization of the bile-duct (Edholm and Jacobson, 1959). Provided sufficient bile containing an adequate concentration of ioglycamate is secreted to replace the volume of bile already in the system, the quantity of ioglycamate excreted is of no importance in intravenous cholangiography. The volume of bile required is unknown but there is a "dead-space" volume since there is a delay between the start of the choleresis induced by the excretion of contrast and its appearance in the bile (Whitney and Campbell, 1972; Whitney and Bell, 1972). Ioglycamate appeared later in the bile when a slow rate of infusion was used. The maximum concentration was not reached until 70 minutes from the start of the infusion at the slower rate, compared with 40 minutes when the faster infusion was used (Fig. 3). The slower infusion rate, however, enabled the duration of the infusion to be increased without increasing the quantity of ioglycamate administered. This produced a prolonged "peak concentration" (Fig. 4), which should enable the whole of the bile in the biliary tree to be replaced by bile containing the maximum concentration of ioglycamate.

A prolonged infusion at a low dose-rate has been suggested for jaundiced patients. If the concentration of ioglycamate in the bile is inadequate for the demonstration of the bile-duct, sufficient contrast may collect in the gall-blader subsequently to provide a satisfactory demonstration of the bile duct when the gall-bladder is made to contract (Hoenig *et al.*, 1970).

The plasma concentration of ioglycamate rises rapidly if the infusion rate greatly exceeds the rate of excretion (Fig. 5) and this would be expected to increase the incidence of toxic effects. In order to minimize this risk the rate of administration should not exceed twice the maximum rate of biliary excretion. Further studies are still required in man to determine the transport maximum of ioglycamate in patients with jaundice.

ACKNOWLEDGEMENTS

This work was in part supported by a grant from Schering A.G. who also supplied the labelled ioglycamate. One of us (G.D.B.) was in receipt of a grant from Weddel Pharmaceuticals. The authors are grateful to Professor R. E. Steiner and Dr. R. H. Dowling for their help, and also to Mr. K. Stephenson for technical assistance.

REFERENCES

Allen, W. M. C., 1969. Drip infusion cholangiography in cases of failed cholangiography. *British Journal of Radiology, 42*, 347–350.

Burgener, F., Halpern, A., Miller, G., Hoenig, V., Preisig, R., and Fuchs. W., 1970. Die Infusionscholangio graphie bei ikterischen Patienten. *Radiology and Clinical Biology, 39*, 175–176.

Cook, D. L., Lawler, C. A., Calvin, L. D., and Green, D. M., 1952. Mechanisms of bile formation. *American Journal of Physiology, 171*, 62–74.

Darnborough, A., and Geffen, N., 1966. Drip infusion cholangiography. *British Journal of Radiology, 39*, 827–832.

Dowling, R. H., Mack, E., Picott, J., Bergen, J., and Small, D. M., 1968. Experimental model for the study of the enterohepatic circulation of bile in rhesus monkeys. *Journal of Laboratory and Clinical Medicine, 72*, 169–176.

Dowling, R. H., Mack, E., and Small, D. M., 1970. Effect of controlled interruption of the enterohepatic circulation of bile salts by biliary diversion and by ileal resection on bile salt secretion, synthesis and pool size in the rhesus monkey. *Journal of Clinical Investigation, 49*, 232–242.

Edholm, P., and Jacobson, B., 1959. Quantitative determination of iodine in vivo, *Acta Radiologica, 52*, 337.

Feldman, M. I., and Keohane, M., 1966. Slow infusion intravenous cholangiography. *Radiology, 87*, 355–356.

Fischer, H. W., 1965. The excretion of iodipamide. Relation of bile and urine outputs to dose. *Radiology, 74*, 483–490.

Foy, R. E., 1968. Slow infusion compared with direct injection cholangiography. *Radiology, 90*, 576–578.

Hoenig,, V., Halpern, A. Fuchs, W. A., Miller, G., and Preisig, R., 1970. Die experimentelen Grundlagen der intravenösen Cholangiographie. *Schweizier Medizinsche Wochenschrift, 100*, 1210.

McNulty, J. G., 1968. Drip infusion cholecysto-cholangiography. *Radiology, 90*, 570–575.

Margolin, F. R., and Obata, W., 1968. Drip infusion intravenous cholangiography. *Radiologia Clinica, 37*, 353–356.

Miller, G., Fuchs, W. A., and Presig, R., 1969. Die Infusionscholangiographie in physiologischer Sicht. *Schweizer Medizinische Wachenschrift, 99*, 577.

O'Maille, E. R. L., Richards, T. G., and Short, A. H., 1966. Factors determining the maximum rate of organic anion secretion by the liver and further evidence on the hepatic site of action of the hormone Secretin. *Journal of Physiology, 186*, 424–438.

Payne, R. F., 1968. Drip infusion cholangiography. *Clinical Radiology, 12*, 291–295.

Sperber, I., and Sperber, G., 1971. The hepatic excretion ot radiocontrast agents. *International Encyclopaedia of Pharmacology and Therapeutics, Section 76, 1*, 165–235.

Taenzer, V., and Herms, H. J., 1971. Intravenöse Cholegraphie mit Biligram. *Fortschritte-Röntgenstrahlen*, 114, 102.

Wheeler, H.. Meltzer, J. I., and Bradley, S., 1960. Biliary transport and hepatic storage of sulfobromophthalein sodium in the unanaesthetised dog, in normal man and in patients with hepatic disease. *Journal of Clinical Investigation, 39*, 1131–1144.

Whitney, B., and Bell, C. D., 1972. Single bolus injection or slow infusion for intravenous cholangiography?—Measurement of iodipamide (Biligrafin) excretion using a rhesus monkey model. *British Journal of Radiology, 45*, 891–895.

Whitney, B., and Campbell, C. B., 1972. Effect of interruption of the enterohepatic circulation of bile on the secretion of iodipamide in the bile of the rhesus monkey. *Investigative Radiology*, 7, 83–87.

Book review

Introduction to Radiotherapy. By Sameer Rafla, and Marvin Rotman, pp. x + 177, 1974 (St. Louis, C. V. Mosby Co.; distributed in Britain by Henry Kimpton, London), £5·70.

This book is written for medical students, technicians and housemen who may wish to know a little more about radiation therapy and oncology. It would also be a useful book for student radiographers.

It covers the physical aspects of the subject including the armamentarium of a department. There is a brief account of departmental organization. The authors then move on to consider aspects of treatment planning in a simple way making use of excellent cross-sectional anatomical diagrams with superimposed fields and isodose contours. In Figs. 3–9 there appears to be an error in that the wedged filter is reversed. This together with two minor errors has been corrected in an errata slip.

Radiation effects in cells and normal tissues, followed by those in tumours are discussed in a concise but adequate way. The section on radiation oncology tackles the various systems, outlining the type of management which can be anticipated and the results obtained. There is an excellent glossary.

This is a small book of only 177 pages. It is well illustrated and indexed and should appeal to those already mentioned.

B. T. Hale.

1976, *British Journal of Radiology*, *49*, 123–125

Septal lines in pure right heart failure

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(*Received June, 1975 and in revised form August, 1975*)

ABSTRACT

Two adult patients are described with pure right heart failure and chronically elevated systemic venous pressure. Neither patient had evidence of pulmonary venous hypertension, but both had septal lines. This unusual finding may be the result of impaired centripetal lymph flow in the lungs due to obstruction of the drainage of the thoracic duct by raised systemic venous pressure.

Septal lines are seen in both cardiac and pulmonary disease. In cardiac disease they are invariably a reflection of pulmonary venous hypertension associated with lesions sited in the left side of the heart or pulmonary veins. They usually disappear rapidly after reduction of the pulmonary venous pressure by medical or surgical treatment. In isolated right heart failure causing an elevated systemic venous pressure, the pulmonary venous pressure is normal and so septal lines would not be expected. We wish to describe two cases in which septal lines have been seen in association with pure right-sided heart failure.

CASE REPORTS

Case 1

A male clerk was found at four years of age to have pulmonary stenosis causing right ventricular hypertophy with a loud systolic murmur in the pulmonary area. Cardiac catheterization revealed mean pressures of 3 mm Hg in the RA, 29 mm Hg in the RV, 15 mm Hg in the infundibulum and 5 mm Hg in the main pulmonary artery. There was no evidence of a shunt. During the next 12 years he remained well, but from the age of seven the JVP was elevated and the liver enlarged.

Then, at 16, he developed peripheral oedema over a fortnight and was admitted to hospital. At no time had he been breathless. Clinical examination revealed no cyanosis or clubbing. There was gross swelling of the scrotum and inner thighs. The JVP was raised to the angle of the jaw with a prominent "a" wave and the liver was large. On auscultation in the pulmonary area there was a harsh ejection systolic murmur. The lungs were clear. A chest radiograph demonstrated a large heart with prominence of the right ventricle and right atrium. The pulmonary vessels were underfilled, and, surprisingly, septal lines were present in the right costophrenic angle, but not on the left side (Fig. 1A and B). Treatment with diuretics effected prompt clinical improvement, the peripheral oedema subsiding and the septal lines on the chest radiograph disappearing (Fig. 1C). However, the elevated JVP and hepatomegaly remained. Cardiac catheterization at this time revealed a mean pressure of 6 mm Hg in the RA, a systolic pressure of 100 mm Hg in the RV and a pressure of 15/5 with a mean of 9 mm Hg in the MPA. Again oxygen saturations were normal with no evidence of a shunt. The angiocardiogram demonstrated a small pulmonary ring with valvar stenosis.

At operation an enlarged right ventricle and atrium were confirmed. The pulmonary valve was diaphragm-like with a small central orifice. A pulmonary valvotomy was performed from which an uneventful recovery was made.

Two weeks later the chest radiograph showed a smaller heart with normal pulmonary vessels. The raised JVP and hepatomegaly returned to normal during the next five years, and he remains well.

Case 2

A male sanitary inspector was well throughout childhood and adolescence. He served overseas during World War II and was graded A1. At that time, at the age of 30, he was conscious of mild dyspnoea on extreme effort, but played football. At 31 he was aware of definite limitation on exercise and once fainted after sprinting 100 yards.

At a routine mass X-ray examination, when 38 years old, he was found to have a large heart and was referred to the National Heart Hospital. His only complaint was dyspnoea with severe exercise. There was no cyanosis, clubbing or oedema, but evidence of right ventricular hypertrophy with a widely split second sound and a loud P2. The JVP was elevated. The chest radiograph demonstrated slight cardiac enlargement with dilation of the pulmonary trunk and proximal pulmonary arteries, but with a reduction in size of the peripheral vessels. Septal lines were visible in both costophrenic angles (Fig. 2A and B). The diagnosis of pulmonary arterial hypertension was made, but the septal lines were unexplained.

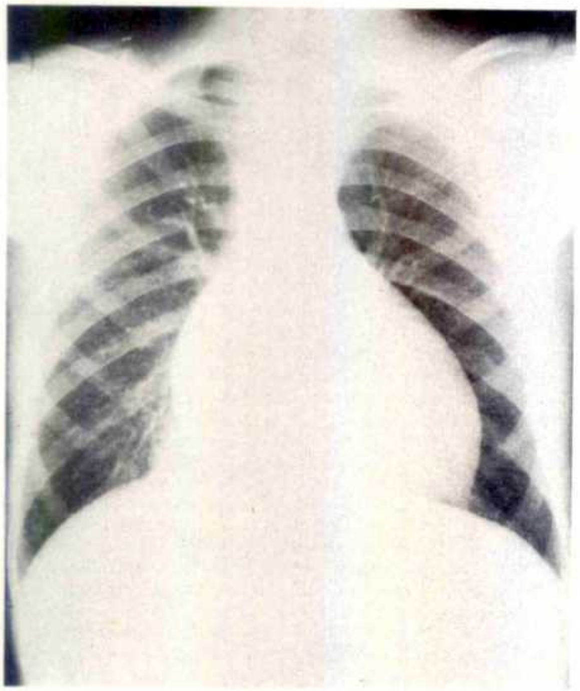
During the next few years he remained well, with no deterioration and in 1957, at the age of 43, cardiac catheterization was performed. This revealed mean pressures of −2 mm Hg in the RA, 70 mm Hg in the RV and 70 mm Hg in the MPA. Attempts to wedge the catheter were unsuccessful. No shunt was demonstrated. The chest radiograph remained unchanged, and the septal lines were still present.

Eight years later the JVP was 6 cm with a prominent "a" wave, and he was again catheterized. The mean pressure was 5 mm Hg in the RA and 75 mm Hg in both the RV and MPA. Again wedging was unsuccessful and there was no evidence on oxygen saturation of a shunt. A pulmonary angiogram demonstrated gross dilation of the main pulmonary artery and proximal branches with marked diminution in size and tortuosity at segmental artery level. In particular, the pulmonary veins and left atrium were normal with no delay in flow across the mitral valve. No shunt was demonstrated. The chest radiograph at this time showed an increase in the number of septal lines in the left costophrenic angle and in the size of the pulmonary trunk and proximal pulmonary arteries. The diagnosis of primary pulmonary hypertension was made.

He was regularly seen in out-patients with no change in his symptoms or signs, but the JVP returned to normal with no treatment.

In 1970, aged 56, he contracted infective hepatitis and became jaundiced with abnormal liver function tests. In October that year he developed a fatal *E coli* septicaemia.

At post-mortem the heart was slightly enlarged, entirely due to right ventricular hypertrophy. The pulmonary trunk and its main branches were enlarged with atheromatous changes. There was no coronary or valvar abnormality. The pulmonary veins and left heart were normal. Evidence was also present of multilobular cirrhosis.



DISCUSSION

The presence of septal lines with isolated right heart disease without pulmonary venous hypertension has not been previously described. It is difficult to explain but some observations may be made from the two cases reported.

(1) Both patients had clinical evidence of long standing RV outflow obstruction (probably longer than 12 years).

(2) The JVP was markedly and chronically elevated with right atrial hypertension.

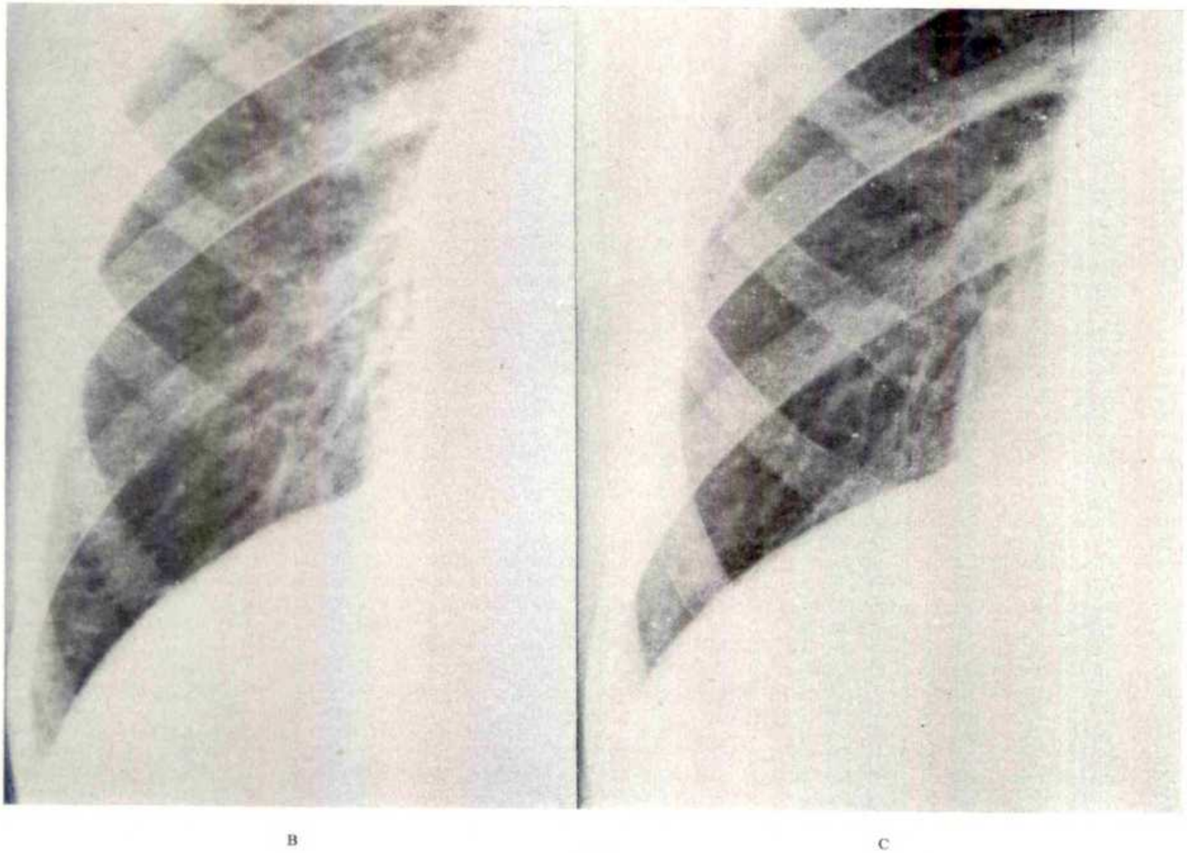
(3) There was no evidence of a right to left shunt at atrial level, even though the RV pressures were approaching systemic values.

FIG. 1. *Case 1.*

(A) Severe pulmonary stenosis. Marked enlargement of the right heart and septal lines at the right base.

(B) Local view of right base showing septal lines.

(C) Local view of right base showing disappearance of septal lines following medical treatment.



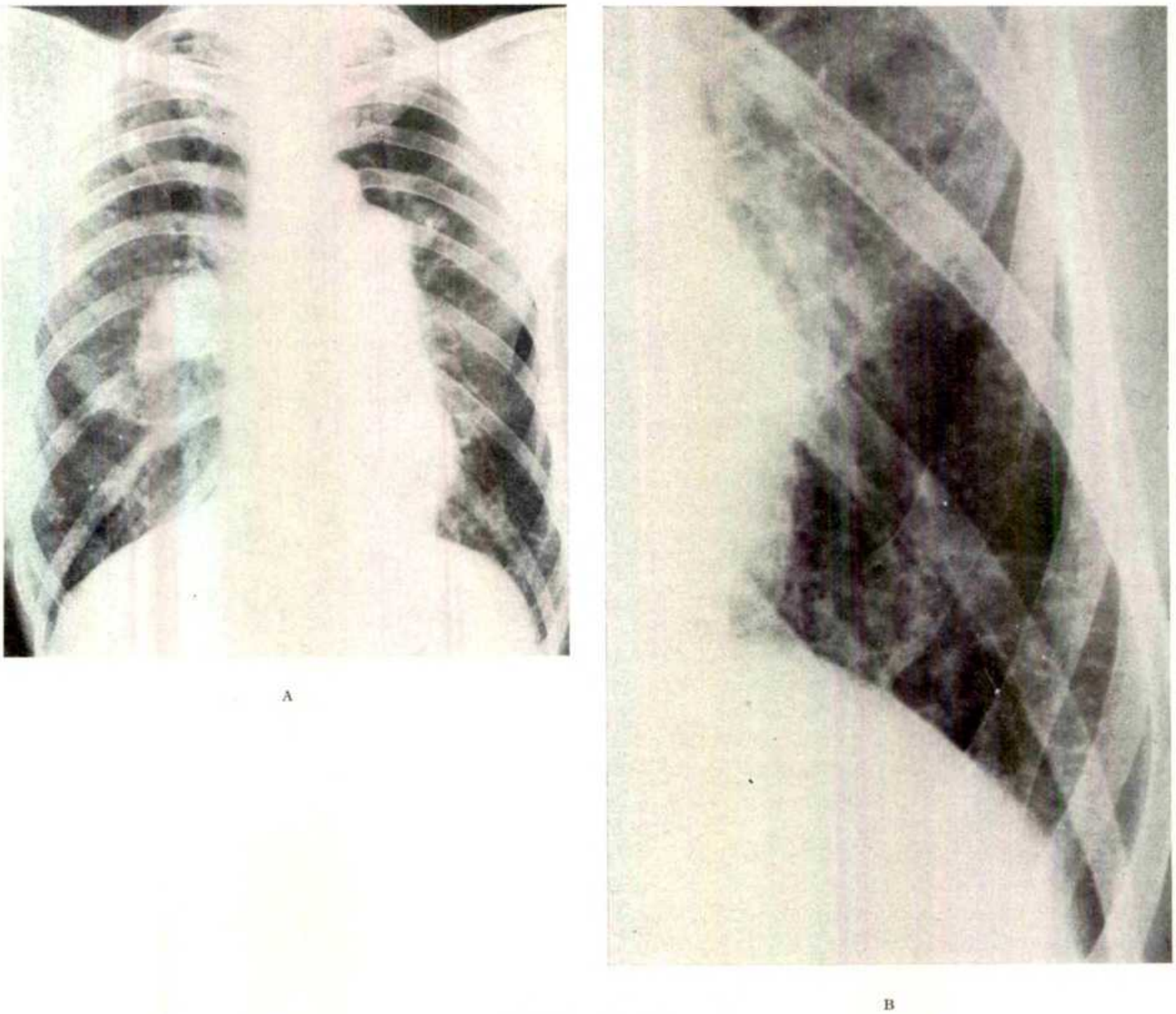


FIG. 2. *Case 2.*

(A) Primary pulmonary hypertension. Enlargement of proximal pulmonary arteries. Bilateral basal septal lines.
(B) Local view of right base showing septal lines.

A possible explanation is that elevation of the systemic venous pressure in the thorax causes obstruction to the drainage of the thoracic duct. This being the case, severe chronic elevation of the systemic venous pressure may cause oedema of the interlobular septa in the lungs, as has been described following obstruction or ligation of the thoracic duct. Thus the septal lines may be the result of impaired centripetal lymph flow in the lungs and not transudation of fluid from the pulmonary capillaries (Grainger and Hearn, 1955; Felson, 1973).

ACKNOWLEDGMENTS

We are grateful to Dr. Wallace Brigden and Dr. Aubrey Leatham for allowing us to publish details of their cases.

REFERENCES

FELSON, B., 1973. *Chest Roentgenology*, pp. 185–250 (W. B. Saunders Co., London).

GRAINGER, R. G., and HEARN, J. B., 1955. Intrapulmonary septal lymphatic lines (B lines of Kerley). *Journal of the Faculty of Radiologists*, 7, 66–76.

1976, *British Journal of Radiology*, *49*, 126–132

Van Buchem's disease
(Hyperostosis corticalis generalisata)

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(*Received May, 1975*)

ABSTRACT

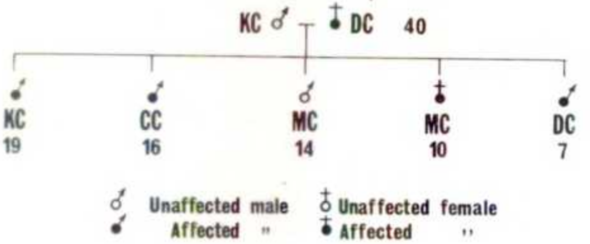
The features of Van Buchem's disease are described, affecting six members of one family, spanning three generations, of ages from 7 to 64 years.

Van Buchem, Hadders and Ubbens (1955) described a bone dysplasia consisting of an increase in cortical bone thickness and density affecting the skull, mandible, and shafts of the long bones. The mandible was greatly thickened and enlarged, with prognathos, the vault of the skull showed thickening and increased density of the inner and outer tables, and the long bones showed cortical thickening of the shafts due to endosteal bone deposition. Scott and Gautby (1974) described changes in the medullary bone of vertebral bodies.

The condition is first detected in childhood and shows a general progression throughout life, but with very little physical disability. The alkaline phosphatase is elevated in about 50 per cent of cases, but no other abnormalities of blood chemistry have been reported. Further cases were described by Fosmoe, Holm and Roscoe (1968), Van Buchem (1971), Maroteaux, Fontaine and Scharfman (1971), and Scott and Gautby (1974), also six probable cases in a Japanese family were reported by Russell, Bizzozero and Omori (1968).

There is a marked familial tendency in this condition (Van Buchem, 1955; 1962; 1971), Worth and Wollin (1966), and Maroteaux *et al.* (1971). This report presents the clinical and radiographic features of six members of one family whose ages range from 7 to 64. One of the patients (Mrs. D. C.) has been the subject of a previous publication (Dyson, 1972). The genealogical table is presented in Table I and the clinical and radiological features are as follows:

TABLE I
GENEALOGICAL TABLE



Mrs. I. B., aged 64 years, mother of Mrs. D. C., showed facial appearances (Fig. 1) similar to her daughter (Fig. 2). Blood chemistry was normal.

Radiographs were reported as follows:

Skull: Dense thickening of the vault and base of the skull, and of body of the mandible, strongly resembling Paget's disease (Fig. 3)

Chest: Scapulae and ribs showed increased density of the cortical bone but normal thickness of the cortex of these bones.

Vertebrae: Appeared normal.

K. C., husband of Mrs. D. C., showed no bony abnormality.

K. C., aged 19 years, son. Complained of nasal blockage, and showed a facial appearance similar to his mother (Fig. 4). Blood chemistry was normal.

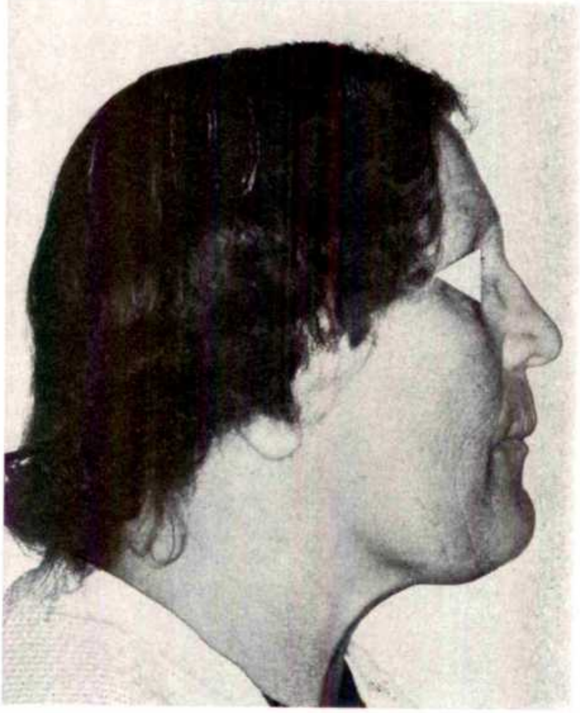


FIG. 1.

Mrs. I. B., large mandible and wide nasal bridge.

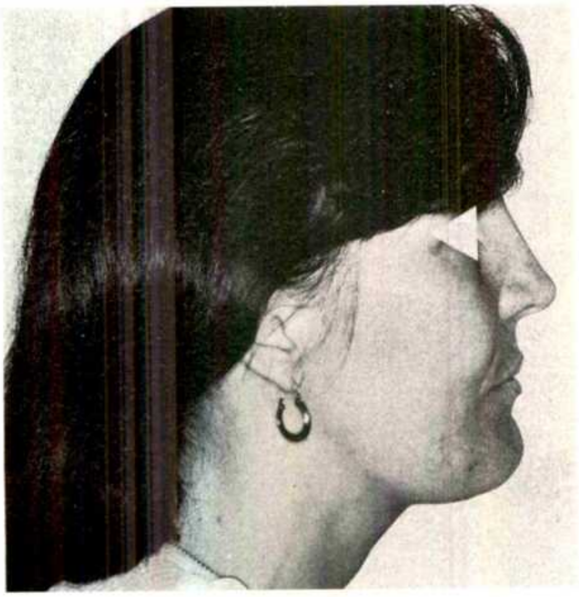


FIG. 2.
Mrs. D. C., features similar to Mrs. I. B.

Radiographs were reported as follows:

Skull: Thickening and increased density of both tables of the vault and base, and in the body of the mandible (Fig. 5).

Skeletal survey: Cortical thickening and increased density which was most marked in the middle third of the shafts of all the long bones and in the ribs (Figs. 6 and 7). The upper thoracic vertebrae showed increased density of cortical bone.

On February 27, 1975, the pelvis showed coarse stellate trabeculation in the region above the acetabula (Fig. 8) similar to that seen in Mrs. D. C. (Fig. 14).

C. C., aged 16 years, son. Facial appearance similar to his mother (Fig. 9).

Radiographs were reported as follows:

Skull: The inner table shows a little thickening and the body of the mandible shows cortical thickening and increased density anteriorly (Fig. 10).

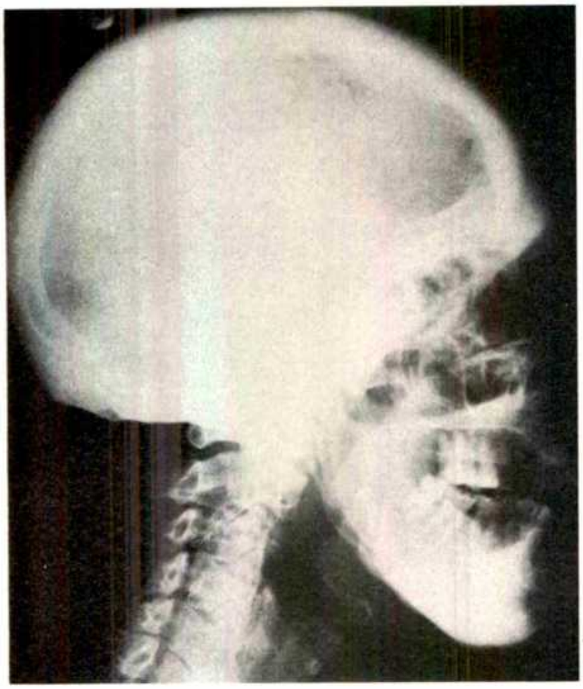


FIG. 3.
Mrs. I. B., skull, showing thick, dense, vault and mandible.

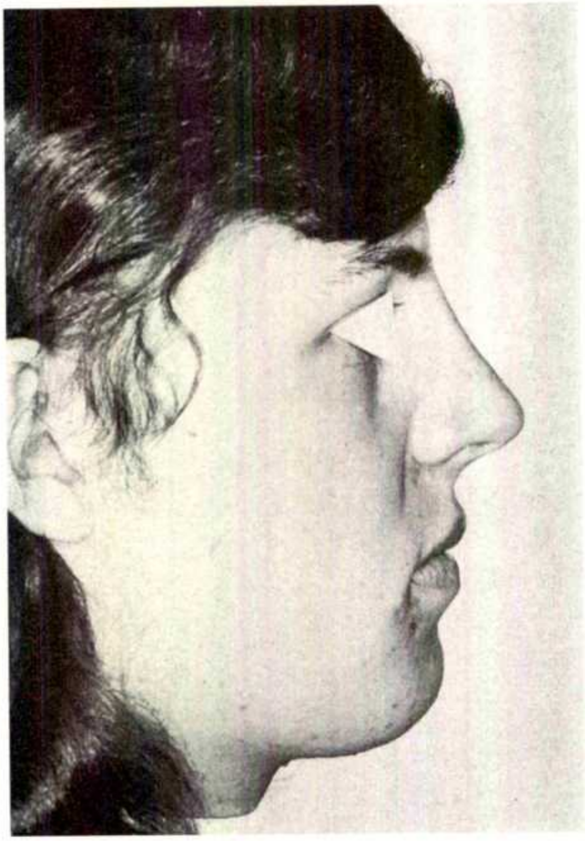


FIG. 4.
K. C., son, facial features similar to his mother.

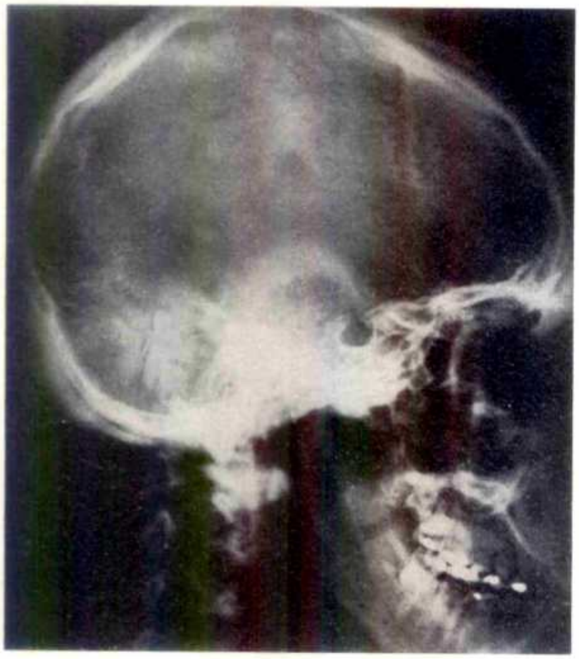


FIG. 5.
K. C., son, skull, showing thickening and increased density of vault and base.

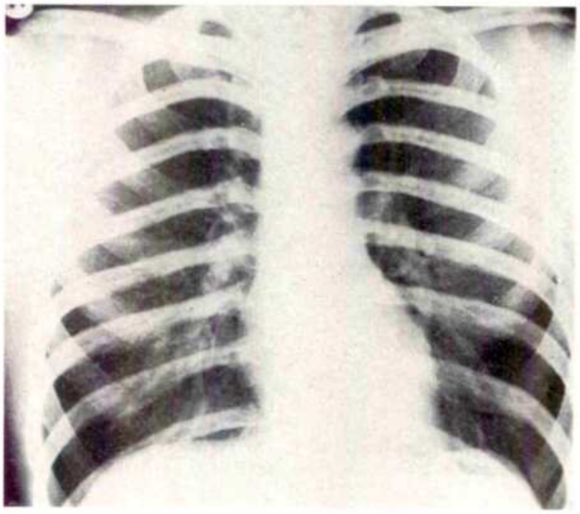


FIG. 7.
K. C., son, chest, showing cortical thickening of the ribs and clavicles.

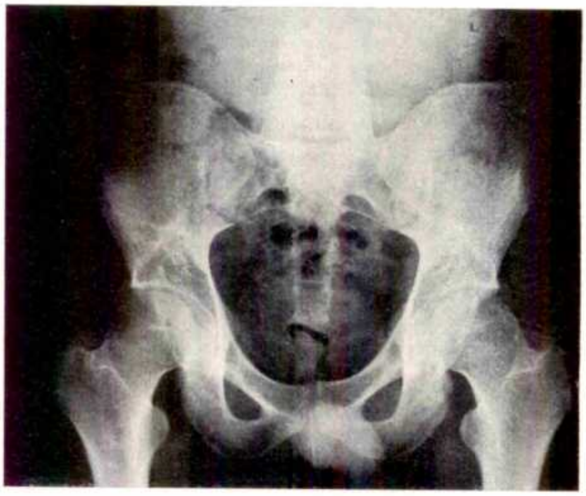


FIG. 8.
K. C., son, pelvis, showing coarse stellate trabeculation around the acetabula.

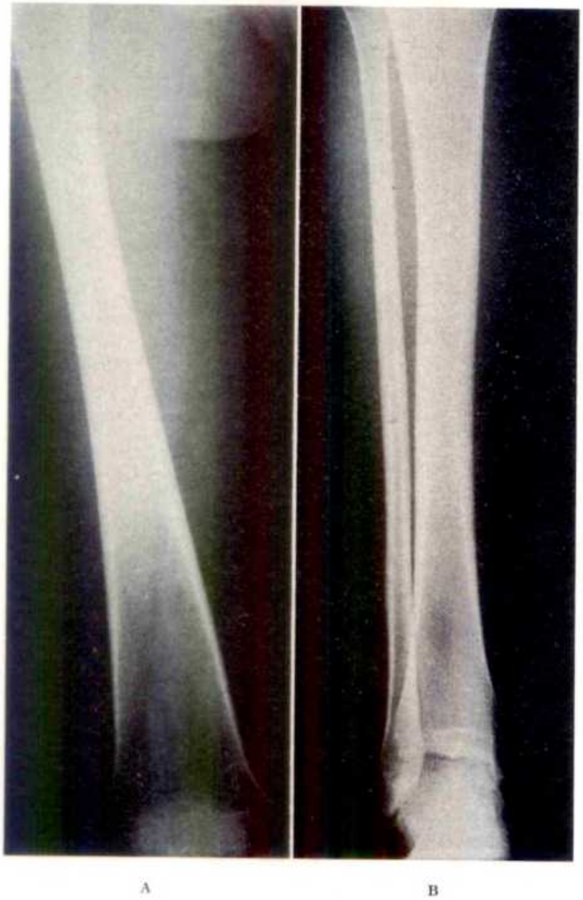


FIG. 6.
K. C., son, long bones, showing cortical thickening of the shafts.

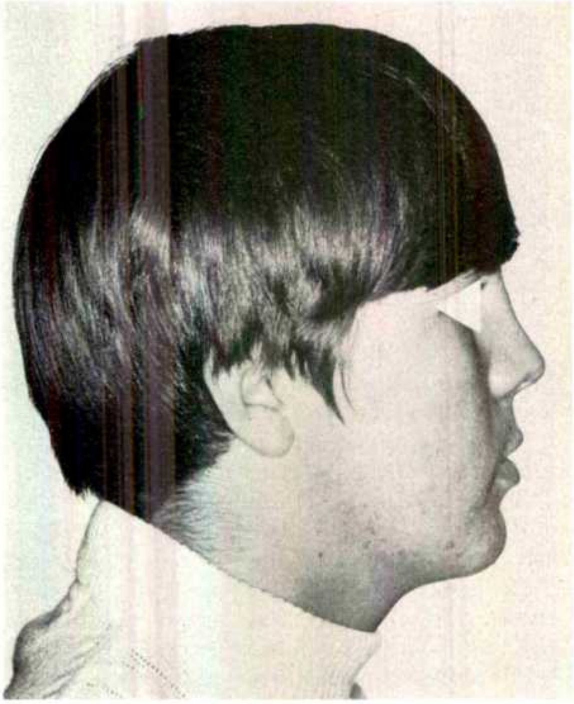


FIG. 9.
C. C., son, facial resemblance to his mother.

Chest: The upper seven ribs on both sides show cortical thickening.
Vertebrae: Showed no abnormality.

M. C., aged 14 years, son. No abnormality. Facial appearance similar to his father.

D. C., aged 7 years, son. Facial appearance resembles his mother.

Radiographs were reported as follows:
Skull: A slight increase in density of cortical bone is seen in the skull and mandible.
Chest: The upper seven ribs on both sides, and the clavicles, all show definite slight cortical thickening and increased density of cortical bone.
Vertebrae: Showed no abnormality.

M. C., aged 10 years, daughter. Showed facial appearance similar to her mother (Fig. 11).

Radiographs were reported as follows:
Skull: Shows a slight increase in density of cortical bone of the inner table of the vault and base. The mandible appears normal.
Chest: The upper seven ribs on both sides and both clavicles all show increased density and slight thickening of cortical bone (Fig. 12).

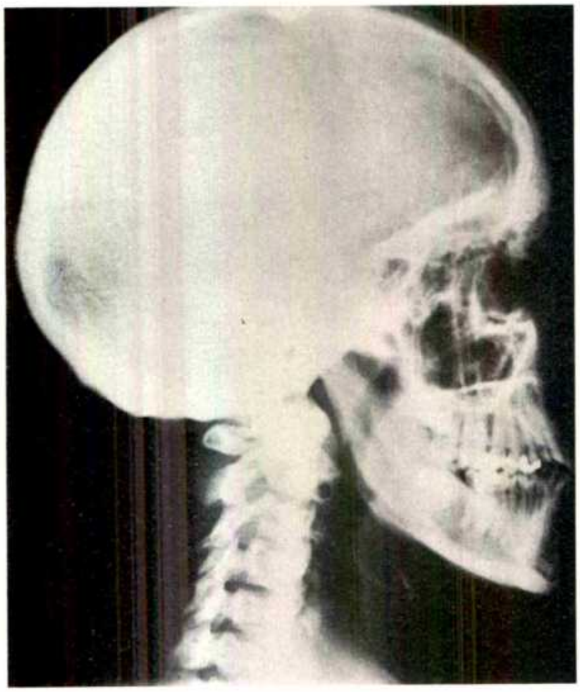


FIG. 10.
C. C., son, skull, showing slight thickening of inner table of skull, and of cortex of the mandible anteriorly.

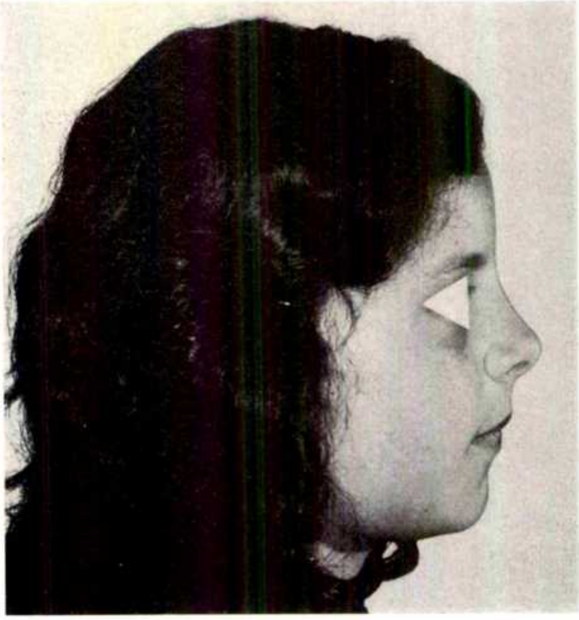


FIG. 11.
M. C., daughter, facial appearance similar to her mother.

Recent radiographs of Mrs. D. C. (March 3, 1973) show:

Skull: Thickening and increased density of the vault and increased density, with expansion of the mandible (Fig. 13). There is no change in appearance since May 1968.

Pelvis: Shows coarse dense trabeculation in the iliac bones around the acetabula (Fig. 14), with a distinctive stellate pattern.

Long bones: All show increased density and thickening of the cortex of the shafts with narrowing of the medullary cavities (Fig. 15).

Vertebrae: Appeared normal.

She complains of pain and swelling of the mandible and increased thickening of the bridge of the nose. Her blood chemistry remains normal.

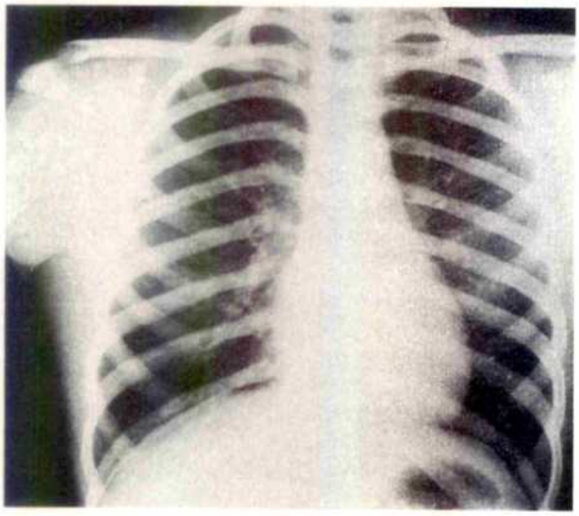


Fig. 12.

M. C., daughter, upper seven ribs and clavicles, showing increased thickness and density of cortical bone.

Discussion

This family demonstrates the progressive development of this disease, from the youngest member of seven years up to the eldest of 64 years.

The familial tendency is evident and has been well documented. The mode of inheritance, however, is not yet clearly established and is, at present, somewhat confusing. Van Buchem noted in 1971 that "the pedigree chart is indicative of the autosomal recessive nature of this disease". On the other hand, Maroteaux observed a dominant transmission. The genealogical table of this affected family also shows a dominant mode of inheritance.

The radiological features are sufficiently characteristic to enable a confident diagnosis to be made. It is therefore, a condition with which radiologists should be familiar in case it is mistaken for another disease process. The differential diagnosis from

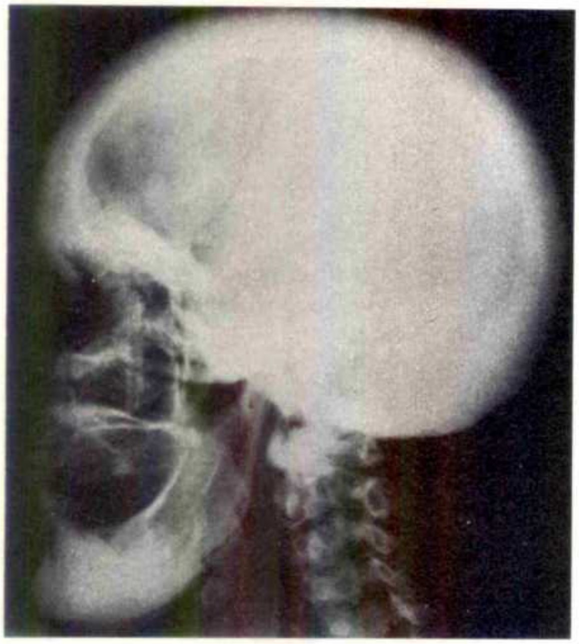


Fig. 13.

Mrs. D. C., skull and mandible, showing gross increase in cortical thickening and density.

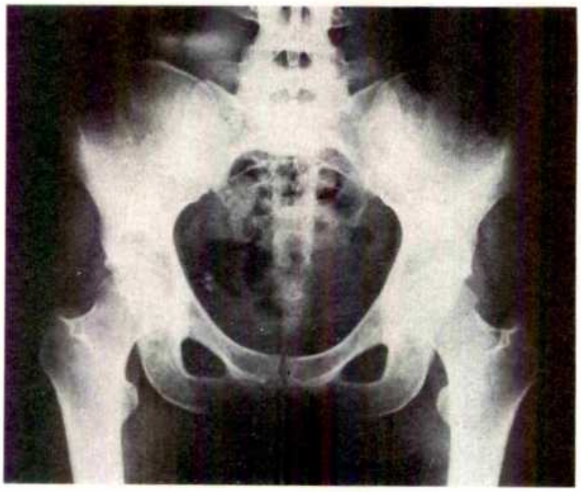
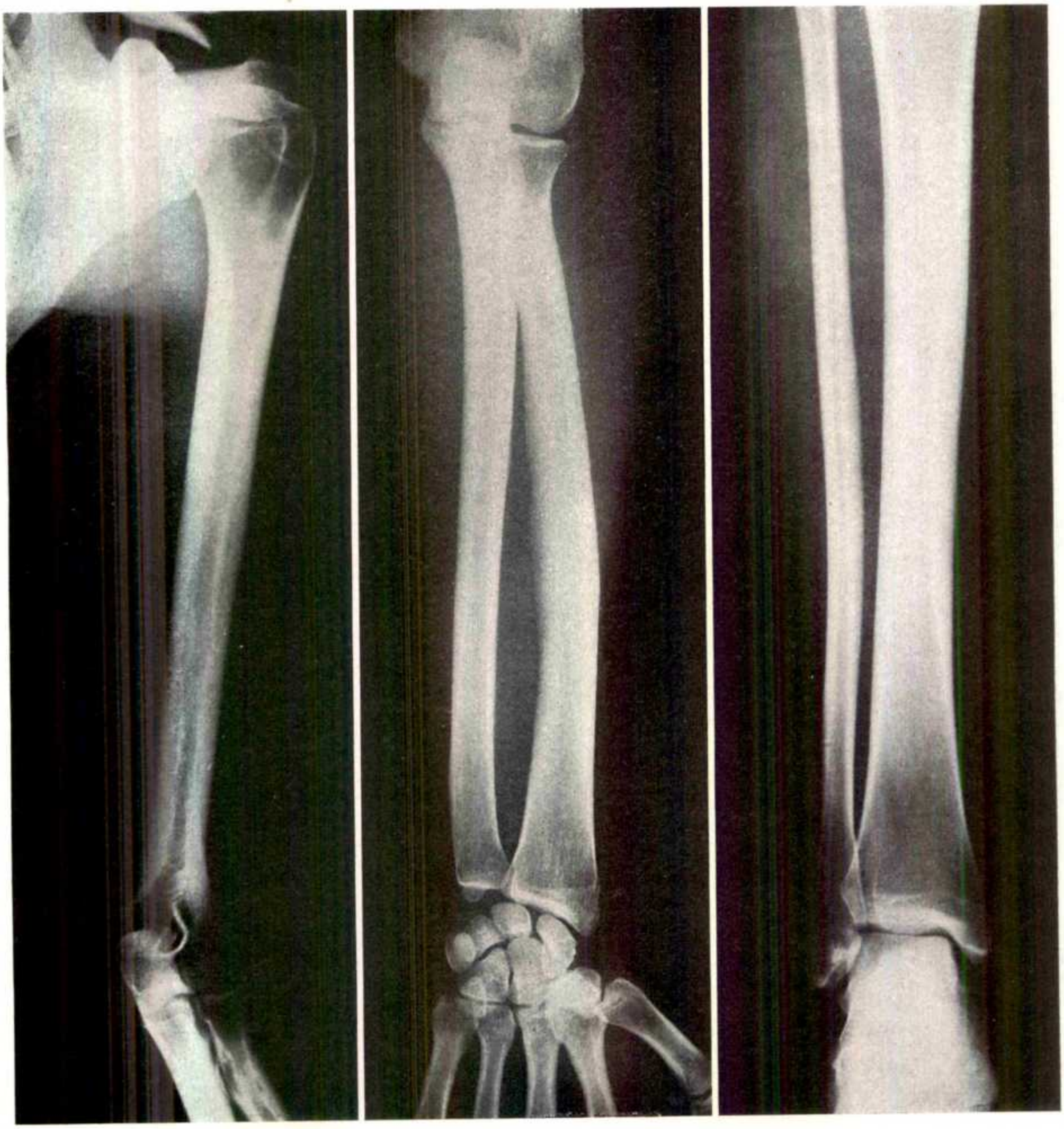


Fig. 14.

Mrs. D. C., pelvis, showing coarse, dense, irregular trabeculation around the acetabula.



A B C

FIG. 15.
Mrs. D. C., long bones, showing thickening and increased density of the shafts, with narrowed medullary cavities.

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TABLE II

COMPARATIVE TABLE OF BONE DYSPLASIAS

	Paget's disease	Osteopetrosis	Diaphyseal dysplasia	Van Buchem's disease
Onset	Late in life.	Childhood.	Childhood.	Early adolescence.
Heredity	Not proved.	Yes.	Yes.	Yes.
Distribution	Any bone. Irregular distribution.	Symmetrical. Long bones in proximal and distal thirds. Ribs. Pelvis. Not mandible.	Symmetrical. Diaphyses of long bones. Not skull.	Symmetrical. Middle thirds of long bone and ribs. Skull. Mandible. Distinctive pattern in pelvis.
Serum Alkaline Phosphatase	Raised considerably.	Normal.	Normal.	Raised in 50 per cent.
Bone pathology	Characteristic pattern with bones softened. Cortical thickening with coarse irregular trabeculation. Areas of osteoporosis and sclerosis.	Bones hard and brittle. No demarcation between cortical and deeper bone. No trabecular structure and no cancellous bone.	Subperiosteal new bone deposition. Fusiform expansion of shafts of long bones. Sclerosis with hypertrophied trabeculae.	Very hard dense normal bone. Endosteal thickening. Narrowed medulla.

Paget's disease, osteopetrosis and Cammurati-Engelman's disease is shown in Table II. It is likely that most cases will come to the attention of a radiologist as an incidental finding at either a screening examination or following injury.

The clinical complications of the condition appear to be of minor type and restricted to the face. One patient complained of nasal blockage and another of increased thickening of the bridge of the nose and pain and swelling of the mandible. Three of the patients suffered from acne.

ACKNOWLEDGMENTS

I am indebted to Mr. M. Tempest, plastic-surgeon, for permission to publish the case reports of these patients, and to Mr. Nigel Pearce, clinical photographer, for the illustrations, also to Mr. D. P. Dyson and Messrs. E. & S. Livingstone for permission to reproduce Figs. 14 and 15 and clinical details from *The British Journal of Oral Surgery*.

REFERENCES

DYSON, D. P., 1972. Van Buchem's disease (hyperostosis corticalis generalisata familiaris). *British Journal of Oral Surgery*, *9*, 237–245.

FOSMOE, R. J., HOLM, R. S., and ROSCOE, C. H., 1968. Van Buchem's disease (hyperostosis corticalis generalisata familiaris). A case report. *Radiology*, *90*, 771–774.

MAROTEAUX, P., FONTAINE, G., and SCHARFMAN, W., 1971. L'hyperostose corticole generalisée. *Archives françaises de pédiatrie*, *28*, 685–698.

RUBIN, P., 1964. *Dynamic classification of Bone Dysplasias Year Book* (Medical Publishers Inc., Chicago).

RUSSELL, W. J., BIZZOZERO, O. J., and OMORI, Y., 1968. Idopathic osteosclerosis. *Radiology*, *90*, 70.

SCOTT, W. C., and GAUTBY, T. H. T., 1974. Hyperostosis corticalis generalisata familiaris. *British Journal of Radiology*, *47*, 503–506.

VAN BUCHEM, F. S. P., 1971. Hyperostosis corticalis generalisata. Eight new cases. *Acta Medica Scandinavica*, *189*, 257–267.

VAN BUCHEM, F. S. P., HADDERS, H. N., HANDSEN, J. F., and WOLDRING, M. G., 1962. Hyperostosis corticalis generalisata. *American Journal of Medicine*, *33*, 387–397.

VAN BUCHEM, F. S. P., HADDERS, H. N., and UBBENS, R., 1955. An uncommon familial systemic disease of the skeleton. *Acta Radiologica*, *44*, 109–119.

WORTH, H. M., and WOLLIN, D. G., 1966. Hyperostosis corticalis generalisata. *Journal of the Canadian Association of Radiologists*, *17*, 67.

1976, *British Journal of Radiology*, *49*, 133–140

The absorbed dose to bone marrow in the treatment of polycythaemia by ^{32}P

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(*Received May, 1975 and in revised form August, 1975*)

ABSTRACT

This paper reports the determination of absorbed dose to bone marrow in the treatment of polycythaemia by ^{32}P, based on the measurement of activities in bone and marrow biopsies taken at various times from 1 to 27 days after injection of the radionuclide. Activities were measured in the cortex, trabeculation and marrow of biopsies taken from the iliac crest, and also in sternal marrow. The biological half-life of ^{32}P in marrow from the iliac crest was found to be nine days; that derived for sternal marrow was lower, but the difference was not statistically significant; the value for trabecular bone was 27 days. The biological half life for ^{32}P in the body, as measured by whole-body counting, was 39 days. Calculations of the dose-rate to trabecular marrow have been made by a method based on that of Whitwell and Spiers (1971), but modified to allow for the presence of ^{32}P in the marrow as well as in trabecular bone. The dose-rates follow a single exponential decay with a half-life of 6·7 days. The integrated dose including that during the first day is 24 rad per mCi injected.

The use of radioactive phosphorus, ^{32}P, as a treatment of primary polycythaemia has been widely adopted since the method was first introduced by Lawrence in 1939 (Lawrence, 1940). Methods for determining the therapeutic dose (in mCi) have varied, but in general they have been empirical and based on the observed clinical response of the red-cell volume (RCV). One method, widely used, has been to give repeated small doses until the desired reduction in RCV is achieved (Reinhard *et al.*, 1946; Lawrence, 1955); another, to give single large doses adjusted according to the patient's weight (Abbatt *et al.*, 1954; Harman, Hart and Ledlie, 1955). A further refinement was introduced by Hume, Cowell and Goldberg (1966), who observed that the fall in RCV was linearly related to the radioactivity given, irrespective of weight, over quite a wide dose range. They were able to use an experimentally-obtained regression line to predict the therapy dose required to reduce the RCV to normal in a given patient provided that his actual and (predicted) normal RCV were known. However, in about 15 per cent of the cases the expected result was not achieved.

Such methods have been evolved largely because little data exists upon which a more fundamental approach, based on radiation dose and biological effectiveness, could be made. Osgood (1965) has compared the effectiveness of intravenous injections of ^{32}P with that of total body irradiation by X rays in the treatment of chronic granulocytic and lymphocytic leukaemias. Calculations of the dose to bone marrow following intravenous administration of ^{32}P have also been made by Seltzer, Kereiakes and Saenger (1964) and by Mays (1973). Low-Beer, Blais and Scofield (1952) produced a dosage scheme based on the assumption that the concentration of ^{32}P, three days after injection, was up to ten times greater in those tissues most avid for phosphorus (bone, liver and spleen), but did not consider whether differences existed in the doses received by these individual tissues. In the present paper the dose to marrow in trabecular bone is determined from contributions by ^{32}P in the marrow itself, in the trabecular bone and in the cortical bone surrounding the trabeculation. Some dose estimates are also made for haemopoietic tissues in other sites.

The determination of the dose-rate to bone marrow is based on the measurement of ^{32}P activity in the bone and marrow of bone biopsies taken at different times after administration of the isotope, followed by dose calculation using methods developed recently (Spiers, 1969; Whitwell and Spiers, 1971; 1975). More realistic dose data are thereby obtained, and these are discussed in the light of earlier estimations.

EXPERIMENTAL PROCEDURES

The subjects were nine patients with primary polycythaemia, clinical details of whom are given in Table I. Four had previously been treated with ^{32}P; the remainder were new, untreated patients. The object of the investigation was explained to each patient and each agreed to take part. The standard procedure adopted was as follows.

Initially red-cell and plasma volumes were measured for each patient by standard techniques,

TABLE I

Clinical details of the patients

Patient	RH	EW	NR	AW	DS	GH	EF	AL	CC
Sex	M	M	F	M	F	M	F	M	M
Age (years)	59	55	67	68	62	48	65	76	46
Weight (kg)	78·0	81·7	69·9	61·9	69·9	64·2	62·0	49·7	77·0
Haemoglobin (gdl^{-1})	20·8	22·7	22·8	19·2	14·0	14·1	17·8	14·4	24·0
Red-cell count $\times 10^{12}$ (l^{-1})	7·6	7·4	7·8	8·8	4·6	6·0	5·8	7·2	6·6
Platelets count $\times 10^{9}$ (l^{-1})	750	525	258	303	415	600	228	280	180
White-cell count $\times 10^{9}$ (l^{-1})	36·2	10·8	8·9	17·7	27	11·3	6·2	7·0	16·0
Blood volume/bodyweight (ml kg^{-1})	111·3	106·9	83·1	107·5	76·0	84·2	81·9	119·3	71·2
Plasma volume/bodyweight (ml kg^{-1})	45·8	38·3	29·7	43·5	47·6	49·2	41·7	61·2	30·1
Red cell volume/bodyweight (ml kg^{-1})	65·5	68·6	53·4	64·0	28·5	35·0	40·2	58·1	41·0
Spleen palpable (cm below costal margin)	7	3	0	5·7	15	Tip	Tip	0	0
Activity administered (mCi)	6·0	6·0	6·0	6·0	3·9	6·1	5·2	3·9	6·1
Previous ^{32}P treatment	no	yes	no	no	no	yes	yes	yes	no
Number of times		2				1	2	5	
Activity per treatment (mCi)		?				3	3	3	
Dates		1964, 68				1970	1970, 71	1968, 69 70, 71, 72	

N.B. Blood values measured on Coulter S and Thrombo Counter.

using ^{51}Cr-labelled red cells plus ^{125}I HSA (ICSH Report, 1973). Six of the patients were then given intravenously 6 mCi ^{32}P and the remainder, for clinical reasons, given smaller quantities. Prior to the ^{32}P injection, each patient's counting-rate was measured on a whole-body radiation counter, and then measured again within half an hour of administration. Whole-body counter measurements were taken at frequent intervals up to 28 days thereafter, and blood samples were also obtained at frequent intervals throughout this period. A trephine biopsy from the anterior aspect of the left iliac crest and a marrow aspirate from the first part of the body of the sternum were taken from each patient.

Whole-body radiation counting

The whole-body retention of ^{32}P was estimated by measuring the Bremsstrahlung emitted from the body using a whole-body radiation counter, made up of eight unshielded NaI (Tl) scintillation detectors housed in a steel cubicle, in a way which has been shown to make its response relatively independent of the distribution of activity in the body (Burkinshaw *et al.*, 1972). The Bremsstrahlung of ^{32}P gives a continuous spectrum, and the total counting-rate above 400 keV was measured, the lower limit being chosen to exclude the γ rays of ^{51}Cr. The counting-rate from the patient was compared with that measured on the same day from an aliquot of the injected dose placed at the centre of the array of eight detectors.

Measurement of blood activity

Whole-blood and plasma samples were measured in an M6 liquid geiger counter,* which was calibrated for its response to ^{32}P in solutions of differing density. The response of the counter to ^{51}Cr and ^{125}I was shown to be insignificant. The separation of plasma from whole blood was completed within an hour of the sample being taken in order to minimize the effect of ^{32}P eluting off the red cells. The activity (μCi/gm) of the blood and plasma were determined by applying density corrections to the count-rates and comparing the results with the count-rate from a ^{32}P standard. Haematocrits were also determined using the standard Wintrobe technique.

Measurement of sternal marrow activity

The sternal marrow aspirate consists of two components, marrow and excess blood. By comparing ^{51}Cr and ^{125}I activities in blood samples and marrow aspirate, allowance could be made for this excess blood. ^{32}P activities were again determined by counting samples in an M6 geiger counter, and ^{51}Cr and ^{125}I activities by counting in a NaI well-counter. The ^{32}P activity (μCi/g) of the sternal marrow could then be obtained.

Measurements of activities in the iliac-crest biopsy

The specimen was received in the laboratory

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*20 Century Electronics Ltd., England.

TABLE II

^{32}P RETENTION IN TERMS OF BIOLOGICAL HALF-LIFE

Patient	Whole body Days	Whole blood		Plasma	
		Fast component Days	Slow component Days	Fast component Days	Slow component Days
RH	41·3	1·4	18·2	—	—
EW	36·3	1·2	17·8	0·3	16·8
NR	34·8	2·4	24·8	—	—
AW	44·0	2·2	24·6	1·5	20·9
DS	37·0	0·6	14·3	—	—
GH	41·4	1·15	21·8	0·4	16·0
EF	33·3	—	—	—	—
AL	38·3	1·9	25·1	1·0	17·7
CC	46·8	2·8	33·3	0·6	28·5
Mean	39·2	1·7	22·5	0·8	20·0
s.d.	4·5	0·7	5·9	0·5	5·1

TABLE III

NORMALIZED ^{32}P ACTIVITIES IN THE STERNAL AND ILIAC CREST BIOPSIES

Patient	Iliac crest biopsy				Sternal marrow aspirate	
	Time after injection (days)	Trabeculation μCi g^{-1}	Cortex μCi g^{-1}	Marrow μCi g^{-1}	Time after injection (days)	μCi g^{-1}
RH	7	0·825	0·137	0·152	—	—
EW	2	0·368 0·389	0·205	0·329	—	—
NR	—	—	—	—	2	0·287
AW	7	0·289 0·194	0·186	0·344 0·203	2	0·283
DS	1	0·390	0·429	0·555	7	0·339
GH	1	0·316 0·465	0·359	0·455 0·341	7	0·355
EF	15	0·415 0·209	0·129	0·122 0·170	13	0·176
AL	10	0·194 0·296	0·304	0·144 0·087	10	0·048
CC	27	0·235 0·163	0·045	0·066 0·051	27	0·028

shortly after removal. The surface fluids and extraneous tissues were gently removed from the biopsy specimen with filter papers and the specimen (approximately 1·5 cm long and 0·5 cm diameter) cut into trabecular portions and a cortical slab. Each trabecular portion was then placed in a wire mesh cage suspended in a conical flask and the marrow cavity tissues flushed out with an air-pressurized water-spray and collected in the flask. The washings were evaporated to 2 ml., dissolved in 10M nitric acid and measured in an M6 counter. The trabecular portions and untreated cortical slab were separately dissolved in nitric acid and similarly measured. Activities in μCi/g were calculated for trabecular bone, cortical slab and marrow.

RESULTS

The results of the procedures described in the

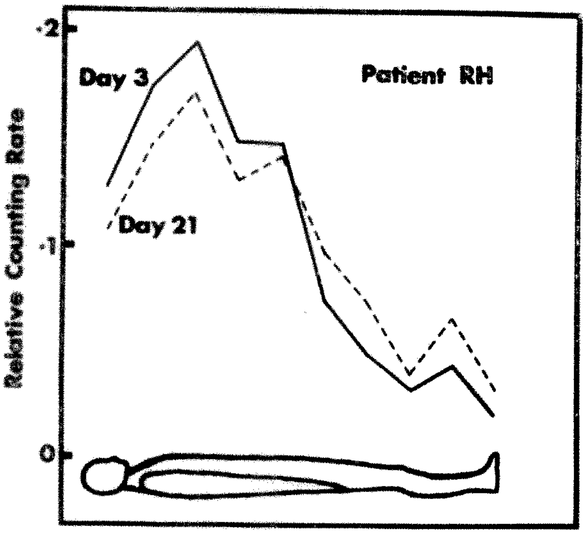

Fig. 1.

Variation of counting-rate along the body at Day 3 and Day 21 for patient RH.

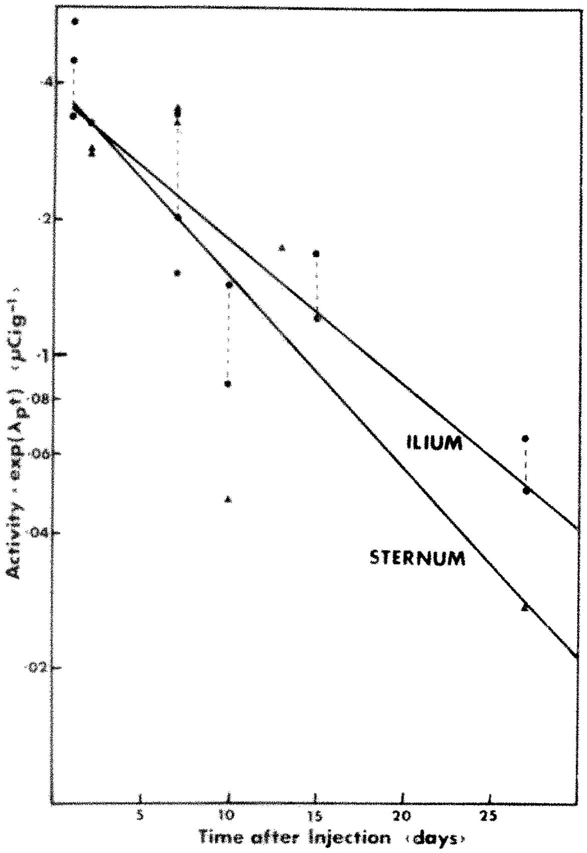

Fig. 2.

Activities in aspirated sternal marrow ($\lambda_B = 0{\cdot}0976 \pm 0{\cdot}0311$ (s.e.) d^{-1}) and in marrow removed from iliac crest biopsy ($\lambda_B = 0{\cdot}0720 \pm 0{\cdot}0114$ (s.e.) d^{-1}), all activities adjusted to time $t=0$. The broken lines link points determined for the same patient (the trabecular portion having been divided into two parts).

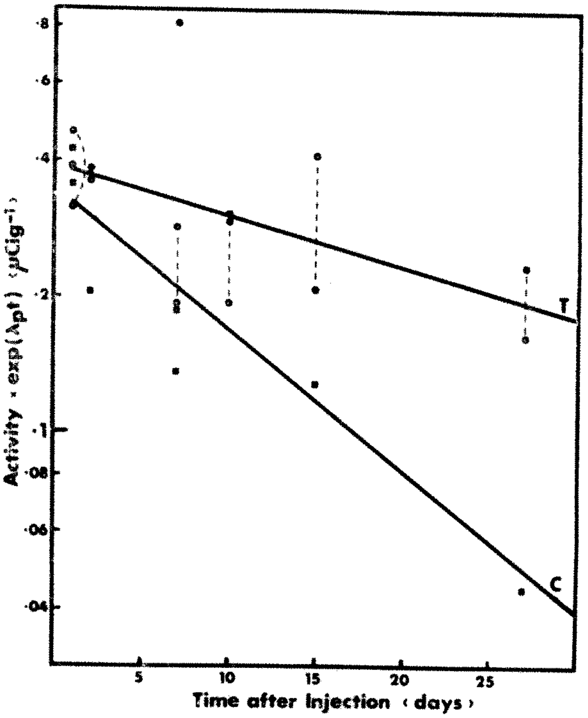

Fig. 3.

Activities in trabecular bone, *T*, ($\lambda_B = 0{\cdot}0260 \pm 0{\cdot}0119$ (s.e.) d^{-1}) and cortical slab, *C*, from iliac crest biopsy; all activities adjusted to time $t=0$. Again the broken lines link points determined for the same patient.

previous sections are summarized in Tables II and III and in Figs. 1–3. In order to compare the activities in different patients it was necessary to adopt some method of normalization. In the first place all ^{32}P activities were adjusted to 6 mCi administered activity. The patients differed, however, in weight, stature and in other ways, as shown in Table I. Bearing in mind the findings of Hume *et al.* (1966) that weight alone was an unsatisfactory basis on which to adjust the administered activity, it was decided to normalize the results to a fixed total plasma volume, taken as 2·94 *l*—the average value for patients seen in the Leeds Clinic. The question of "normalization" will be discussed further at the end of this paper, but it was considered reasonable to normalize by plasma volume because our results are then expressed as those for the same initial activity per litre of plasma—*i.e.* for tissues initially offered the same radionuclide concentration.

Retention of ^{32}P in blood, plasma and whole body

The retention curves of activity in the whole blood and plasma were analysed to determine the biological half-lives. In each case a two-component exponential function was assumed and the exponents estimated by a statistically weighted (1/activity^2) least squares method. The results, which show fast (~one day) and slow components, are given in Table II. Patient EF did not have serial blood samples taken, and the plasma-activity retention curves were not estimated for patients RH, NR and DS because the plasma was not separated sufficiently quickly from some of the blood specimens.

On the other hand, the retention curves for the whole-body activity measurements were found to follow single exponential functions from day one onwards; the whole-body half-lives are also given in Table II.

Retention as a function of anatomical position

In addition to the whole-body counting measurements the gross distribution of ^{32}P was also measured in three of the patients, using collimated γ-ray detectors placed beneath the supine patients. Figure 1 shows how the counting-rate varied along the body of one of the patients at three and 21 days after injection. The other two patients gave similar patterns. The distributions changed gradually with time and in each case the counting-rates over the extremities fell more slowly than those over the trunk. In fact, the relative counting-rate over the extremities, after allowing for physical decay, increased with time, indicating ^{32}P accretion in these parts. Redistribution of ^{32}P continued during the measurements, but since most of the activity was in the trunk, the whole-body effective half-life remained close to that measured over the trunk.

Activities in the sternum and iliac crest biopsies

The activities in marrow from the sternum and iliac crest are shown in Table III and Fig. 2, where it can be seen that the results for each site can be treated as a single group. Single exponential functions have therefore been fitted to each set of values (by least squares on the logarithms of the values). The two values of the biological half-life thus obtained, ~9 days for iliac marrow and ~7 days for sternal marrow, however, do not differ significantly ($P > 0{\cdot}9$).

The activities measured in the trabecular bone and the cortical slab from the iliac crest are shown in Fig. 3. (The cortical slab consists mainly of cortical bone, with some adhering soft tissue and trabecular bone edges.) Best-fit curves are also shown in Fig. 3 for the trabecular and cortical slab activities.

DOSIMETRY

Recent methods of calculating the dose to red marrow from radionuclides incorporated in bone (Whitwell and Spiers, 1971; 1975) can be applied in a modified form to the present cases, where radionuclide activity is also found in the bone marrow. The calculations were designed to determine the average dose-rate to the red marrow at the time of the bone biopsy and hence to study the variation of dose-rate with time after injection. This inevitably involves certain assumptions: first that the activities per gram measured from the iliac specimens of marrow, trabecular bone and the cortical slab are representative of the activities in other corresponding parts of the skeleton; and second that the patients behave as a homogeneous group in respect of uptake, location and retention of the radionuclide. The measured activities were multiplied by average skeletal dose factors, derived from the data of Whitwell and Spiers, to give average red-marrow dose-rates on the biopsy day.

Dose from activity in trabecular bone, cortical bone and marrow

In calculating the dose to bone marrow, the dose factors given by Whitwell and Spiers cannot be applied directly because they relate only to deposition of the radionuclide in the trabeculae. No method has so far been given for the situation in which two inter-penetrating non-equilibrium depositions (in the trabeculae and in the marrow) co-exist. The principle by which the combined dose-rate from both trabecular and marrow activities can be calculated is shown in Fig. 4. If the trabecular activity is greater than the marrow activity, as in

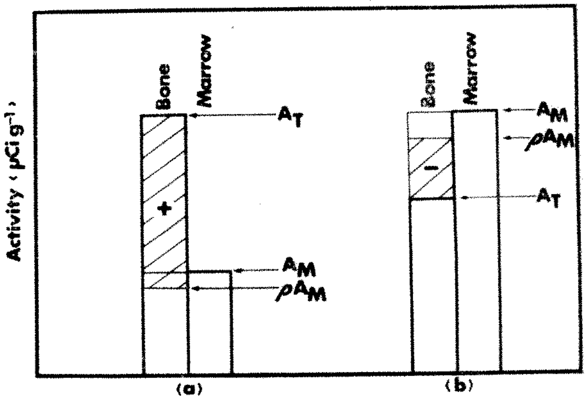

FIG. 4.

Diagram illustrating principle of calculating the combined dose-rate to marrow from activity A_T in the trabecular bone and A_M in the marrow.

Fig. 4a, we could first calculate the dose rate from an "infinite" medium having a notional activity, A_M, equal to that of the marrow, and then add on the dose-rate from the excess activity, $A_T - A_M$, in the trabeculae, where A_T is the trabecular activity. This procedure is not quite exact, however, because the mass stopping power in bone is less than in marrow and, consequently, a smaller activity, ρA_M, in bone will give the same dose to a small mass of tissue within bone as will activity A_M in a uniform soft-tissue medium. The excess bone activity should therefore be adjusted to $A_T - \rho A_M$, where ρ is the ratio of the particle mass stopping powers, bone/marrow. The value of ρ varies slowly with β-particle energy, and has been calculated to be 0·90 for ^{32}P from the data of Berger and Seltzer (1966), assuming that the mass stopping power of marrow is the same as that of muscle.

The first part of the combined dose-rate is calculated from the usual formula:

$$D_1 = 51{\cdot}2 \bar{E}_\beta A_M \text{ rad/day} \quad . \quad . \quad (1)$$

where the activity is in μCi/g and $\bar{E}_\beta$ is in MeV ($\bar{E}_\beta = 0{\cdot}695$ for ^{32}P). The second part of the combined dose-rate is given by:

$$D_2 = \bar{G} D_0 (A_T - \rho A_M) \text{ rad/day} \quad . \quad (2)$$

where $\bar{G}$ is the average dose factor for skeletal red marrow in trabecular bone ($=0{\cdot}276$ for ^{32}P) and D_0 is the dose-rate to a small tissue inclusion from 1 μCi/g of ^{32}P in surrounding bone having dimensions greater than the β-particle range ($=39{\cdot}5$ rads/day), taken from the data of Whitwell and Spiers (1975).

The dose-rate D_{MT} from the combined activities in both marrow and trabeculae is then:

$$D_{MT} = D_1 + D_2 \quad . \quad . \quad (3)$$

If the activity in the marrow is greater than that in the trabeculae, a similar procedure is followed, which is illustrated in Fig. 4b, but the value of D_2 is negative. It must be emphasized that D_1 and D_2 are notional dose-rates used to calculate the combined dose rate D_{MT}, and do not represent the actual contributions to the dose-rate from the marrow and trabecular activities. These can be deduced, however, once D_{MT} is known.

The contribution from the trabecular activity is:

$$D_T = \bar{G} D_0 A_T = 10{\cdot}9 A_T \text{ rad/day} \quad . \quad (4)$$

and hence that from the marrow activity is:

$$D_M = D_{MT} - D_T = (51{\cdot}2 \bar{E}_\beta - \rho \bar{G} D_0) A_M = 24{\cdot}5 A_M \text{ rad/day} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

A small contribution to the dose to marrow in trabecular bone is made by the ^{32}P in the cortex. The average value for the cortical dose factor for the skeleton as a whole is 0·052 for ^{32}P (Whitwell, 1973) and hence the contribution D_C from the cortex can be given as:

$$D_C = 0{\cdot}052 D_0 A_C = 2{\cdot}05 A_C \text{ rad/day} \quad . \quad (6)$$

Where necessary a factor (0·96) has been introduced to allow for lack of particle equilibrium in those bones from which a small fraction of the particle energy escapes (Spiers, 1966; Whitwell, 1973).

Calculated dose-rates from 1 to 27 days post injection

Dose-rates have been calculated at the time of the bone biopsy for each patient, using equations (4), (5) and (6), and the measured activities A_T, A_M and A_C. The total dose-rates to bone marrow, $D_T + D_M + D_C$, are shown in Fig. 5, two points being shown (linked by broken lines) for the five cases when two measurements of A_T and A_M were

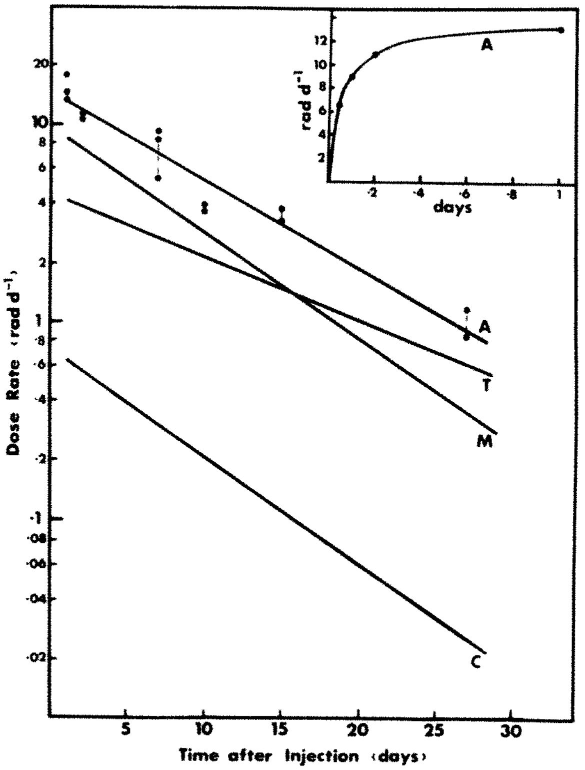

FIG. 5.

Curve A: Best fit single exponential to the total dose rates to skeletal bone marrow ($D_T + D_M + D_C$).
(Curves T, M and C) Best fit curves for the dose-rate contributions from trabecular bone, marrow and cortex respectively.
Insert: Approximate total dose rates calculated for first day.

made. The variation of dose-rate with time, t, from Day 1 can be represented reasonably well by $D=D_1e^{-\lambda t}$ (Curve A), where $D_1=13{\cdot}4\pm0{\cdot}4$ rad/day and $\lambda=0{\cdot}103\pm0{\cdot}007$ day^{-1}, *i.e.* a half-life of 6·7 days. The bone marrow dose integrated on this basis from Day 1 to infinity is then 130±9·7 rads.

If the dose-rate equations (4), (5) and (6) are applied to the best-fit curves for the iliac crest activities in Figs. 2 and 3, the separate contributions to the total marrow dose rate are as shown in Curves T, M and C in Fig. 5. The integrated bone-marrow doses from Day 1 are then 57·6, 71·2 and 5·5 rad respectively for the trabecular, marrow and cortex activities, giving a total integrated dose of 134 rad close to the value obtained from the single exponential analysis above.

Dose received during the first day

No measurements of bone and marrow activities were made earlier than Day 1 but they have been deduced approximately by considering the activities in these tissues at Day 1 together with the measured activities in plasma and whole blood at 0·1 and 0·2 days. It was evident that the bone-marrow and bone activities increased rapidly after injection, and the dose-rates deduced are approximately as in the inset to Fig. 5. The dose contribution, integrated over the first day, was calculated to be ~12 rads.

DISCUSSION AND CONCLUSIONS

Some further consideration should first be given to the method of normalizing the results to a fixed plasma volume of 2·94 *l.* Other procedures are possible and for example, normalization to a standard bodyweight is frequently used. In our case normalization by weight would lead to marrow dose-rates as shown in Fig. 6. This would not much affect the integrated dose but, of the individual patient dose-rates, that for patient AL would appear anomalously low. Apart from his rather low bodyweight, and the fact that he had had previous ^{32}P treatments, this patient was not in other clinical respects different from the other patients investigated. We think, therefore, that the low dose-rate shown for this patient in Fig. 6 is more probably due to the method of normalizing than to any more fundamental cause.

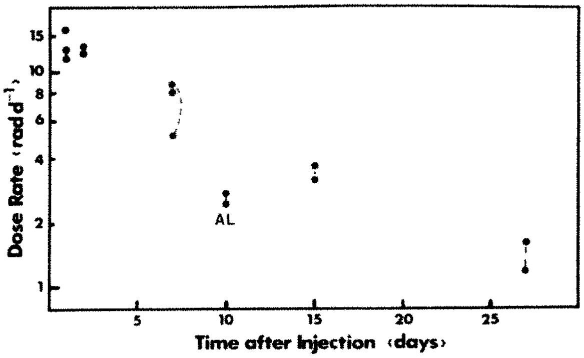

FIG. 6.

Total dose-rates calculated on the basis of normalization by body mass.

The results of our investigations suggest that the total absorbed dose to marrow in trabecular bone is 142 rad per treatment, *i.e.* about 24 rad per mCi injected. The contributions to this dose from activity in trabecular bone, marrow and cortical bone are respectively 10, 13, and 1 rad. Contributions to the total dose from activity in the marrow and trabeculation are thus very similar, the dose-rate at Day 1 from activity in marrow being about twice that from activity in trabeculation, but falling more rapidly with time. The total dose of 24 rad per mCi injected can be compared with a value of 30 rad per mCi injected reported by Seltzer *et al.* (1964). In their calculation these authors assumed that two-thirds of the injected activity was deposited in a compartment comprising bones, liver and spleen from which it was lost with a biological half-life of 49 days. The dose was apparently calculated on the basis of equation (1) with A_M taken as the mean activity per unit mass in this compartment. Mays (1973) has also calculated the dose from ^{32}P by assuming an "uptake of 20 per cent in the 10 kg total skeleton of standard man and an effective retention half-time of 14·1 days". His value of the "average skeletal dose" is 15 rad per mCi injected. Values given by other authors for the dose to bone range from 20 to 50 rad per mCi injected (ICRP, 1971).

The total dose to marrow of 24 rad per mCi injected found in our investigations may also be compared with a "dose in air" of 15 R deduced by Osgood (1965) as the biological equivalent of 1 mCi ^{32}P. This exposure dose of 15 R can be shown to imply a dose to bone marrow (at a depth of 5 cm) of approximately 18 rad. External irradiation, however, does not necessarily result in the same distribution of dose in body tissues as that from an internal emitter.

The dose to tissues, other than marrow in trabecular bone, cannot be determined from our data, but some estimate of the dose to haemopoietic tissues in bone shafts can be made. Bone shafts contain only sparse trabeculation, and any red marrow present would be unlikely to contain more ^{32}P activity than red marrow in normal sites. An approximate dose-rate calculation at Day 1 can therefore be made using equation (1) and assuming the measured value for A_M at that time. The effective half-life would be approximately that for trabecular marrow, and the total dose from Day 1 would be about 112 rads, including a small cortical contribution. The total dose would then be about 125 rad or about 20 rad per mCi injected. Similar considerations suggest that the dose to extra-medullary haemopoietic tissues, as in liver and spleen, would not be higher than the estimated value of 20 rad per mCi injected for marrow in bone shafts.

Finally, it can be seen from Table II that the whole-body biological half-life has a mean value of 39·2 days with a standard deviation of 4·5 days. It is suggested that if the whole-body half-life as determined by whole-body radiation counting lies in the range 39±9 days, the dose to trabecular marrow should be approximately that found in these investigations—24 rad per mCi ^{32}P injected. Because the whole-body counting-rates were found to be accurately represented by a single exponential function, the half-life can be readily determined by a few clinically convenient measurements.

ACKNOWLEDGEMENTS

Acknowledgement is made by four of us (FWS, AHB, SDK and LB) to the Medical Research Council under whose auspices part of the work was undertaken. We are also grateful to Miss D. W. Krupowicz for carrying out measurements with the whole-body counter.

REFERENCES

Abbatt, J. D., Chaplin, H., Darte, J. M. M., and Pitney, W. R., 1954. Treatment of polycythaemia with radioactive phosphorus; haematological studies and preliminary clinical assessment. *Quarterly Journal Medicine, 23*, 91–104.

Berger, M. J., and Seltzer, S. M., 1966. In *Tables of energy losses and ranges of electrons and positrons, NASA SP–3036* (National Bureau of Standards, Washington D.C. 20230).

Burkinshaw, L., Marshall, D. H., Oldroyd, B., and Oxby, C. B., 1972. Optimization of a whole-body radiation counter wth eight detectors. In *Assessment of Radioactive Contamination in Man*, pp. 165–178 (IAEA, Vienna).

Harman, J. B., Hart, P. L. de V., and Ledlie, E. M., 1955. Treatment of polycythaemia with radioactive phosphorus. *British Medical Journal, 1*, 930–934.

Hume, R., Cowell, M. A. C., and Goldberg, A., 1966, Prediction of the dose of radioactive phosphorus in the treatment of polycythaemia vera. *Clinical Radiology, 17*, 295–298.

International Commission on Radiological Protection, 1971. *Protection of the patient in radionuclide investigations*, p. 64. ICRP Publication No. 17 (Pergamon Press, Oxford).

International Committee for Standardization in Haematology (ICSH), 1973. Standard techniques for the measurement of red cell and plasma volume. A report by the Panel on Diagnostic Applications of Radioisotopes in Haematology. *British Journal of Haematology, 25*, 801–814.

Lawrence, J. H., 1940. Preliminary report on a new method for treatment of leukaemia and polycythaemia. *Radiology, 35*, 51–60.

1955. Polycythaemia. Physiology, diagnosis and treatment based on 303 cases. In *A Modern Medical Monograph* (Grune and Stratton, Inc., New York and London).

Low-Beer, B. V. A., Blais, R. S., and Scofield, N. E., 1952. Estimation of dosage for intravenously administered ^{32}p. *American Journal of Roentgenology, 67*, 28–41.

Mays, C. W., 1973. Cancer induction in man from internal radioactivity. *Health Physics, 25*, 585–592.

Osgood, E. E., 1965. The relative dosage required of total body X-ray versus intravenous ^{32}P for equal effectiveness against leukaemic cells of the lymphocytic series or granulocytic series in chronic leukaemia. *Journal of Nuclear Medicine, 6*, 421–432.

Reinhard, E. H., Moore, C. V., Bierbaum, O. S., and Moore, S., 1946. Radioactive phosphorus as a therapeutic agent. *Journal of Laboratory and Clinical Medicine, 31*, 107.

Seltzer, R. A., Kereiakes, J. G., and Saenger, E. L., 1964. Radiation exposure from radioisotopes in paediatrics. *The New England Journal of Medicine, 271*, 84–90.

Spiers, F. W., 1966. Dose to Bone from ^{90}Sr: Implications for the setting of the maximum permissible body burden. *Radiation Research, 28*, 624–642.

Spiers, F. W., 1969. Beta particle dosimetry in trabecular bone. In *Proceedings of an International Symposium on Delayed Effects of Bone-Seeking Radionuclides*, Eds. C. J. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Strover, J. H. Dougherty, and G. N. Taylor, pp. 95–108 (University of Utah Press, Salt Lake City).

Whitwell, J. R., 1973. Ph.D. Thesis, University of Leeds.

Whitwell, J. R., and Spiers, F. W., 1971. The dosimetry of β emitters in bone, theoretical methods. In *Proceedings of the Fifth Congress of the French Society for Radioprotection, Grenoble, France*, pp. 401–417.

1975. Calculated β-ray dose factors for trabecular bone. *Physics in Medicine and Biology* (in press).

Book review

Textbook of Anatomy and Physiology in Radiologic Technology. By Charles A. Jacobi, 2nd edn, pp. xvii+437, 1975 (C. V. Mosby, distributed by Henry Kimpton Publishers), £7·00.

This book is written for radiographers and aims to relate anatomy and physiology to their routine work.

There are some excellent tables throughout the book, and the sections on pathology, injuries and technique will be of interest to the student. Unfortunately, many radiographs and skeletal photographs used as illustrations are poorly reproduced, and there is a noticeable lack of clear diagrams.

There are other anatomy and physiology texts which are more suitable at a similar price.

Miss C. Christie Smith.

1976, *British Journal of Radiology*, *49*, 141–147

Therapeutic irradiation of the central nervous system using intrathecal ^{90}Y–DTPA

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(*Received April, 1975*)

ABSTRACT

The eradication of established neuroleukaemia is often difficult, and with subsequent relapses even harder. The use of an intrathecally-injected β emitting isotope has the advantage of preserving the bone-marrow of the vertebral column and cranium whilst irradiating the meninges. The value of intrathecal ^{90}Y–DTPA (diethylene-triamine penta-acetic acid) has been investigated in nine patients with neuroleukaemia or CNS involvement in malignant lymphoma.

Measurements of retention of the isotope in the whole body, spinal, and intracranial subarachnoid spaces have been made, together with blood levels, and are reported.

The clinical results are presented. In three out of five evaluable patients ^{90}Y–DTPA failed to maintain a chemotherapy-induced CNS remission and in two out of two evaluable patients malignant cells were not dispersed from the CNS with a single intrathecal injection of ^{90}Y–DTPA. It is concluded, therefore, that with this agent and the doses used no useful clinical result is gained.

External irradiation to the central nervous system (CNS) during the first few weeks of remission of acute lymphatic leukaemia (ALL) is now an established procedure aimed at eradicating residual leukaemia in the CNS and so preventing CNS relapse (Hustu *et al.*, 1973). The eradication of established neuroleukaemia is difficult. Aur *et al.* (1972), reported five patients with CNS relapse following 2,400 rad craniospinal irradiation for neuroleukaemia, but all had temporary clearing of the blasts from the spinal fluid.

Willoughby (1974) has, however, reported encouraging preliminary findings of the MRC Working Party for Childhood Leukaemia, which suggests eradication of neuroleukaemia may be achieved with cranial irradiation to 2,500 rad, and spinal irradiation to 1,000 rad after a minimum of six intrathecal injections of methotrexate (10 mg/cm^2).

External irradiation has the immediate disadvantage of producing bone-marrow depression so limiting the amount of chemotherapy which can be given during the same period. Any long-term effects, especially with young children, due to irradiation of the CNS and other structures may become increasingly important with the substantial improvement in survival figures for ALL.

The use of an intrathecally injected β emitting radionuclide to irradiate the CNS has the advantage of restricting the radiation dose to the CNS. We have investigated the use of ^{90}Y chelated to DTPA (diethylene-triamine penta-acetic acid) for this purpose in nine patients with established meningeal disease.

^{90}Y is a pure β-emitting isotope (average energy of β-rays 0·93 MeV) with a half-life of 64 hours. In order to determine the retention and distribution quantitatively by external monitoring ^{169}Yb–DTPA, which emits γ rays of energy 177 and 198 keV and has a half life of 32 days, is administered with the ^{90}Y–DTPA (Wagner *et al.*, 1970). After leaving the cerebrospinal fluid (CSF) the ^{90}Y–DTPA distributes throughout the extracellular fluid and is excreted rapidly by glomerular filtration.

MATERIALS AND METHODS

The ^{90}Y–DTPA and ^{169}Yb–DTPA were supplied by the Radiochemical Centre, Amersham, U.K. The ^{90}Y is carrier free (100 mCi/μgY) and the ^{90}Y-chelate contains 0·1 mg DTPA per mCi of ^{90}Y. Purity was checked by chromatography (Kovach, 1973): less than 2 per cent of the ^{90}Y and 1 per cent of the ^{169}Yb was in the ionic form.

Whole-body retention was measured by serial counting in a whole-body counter with the patient lying prone and then supine 2 m below a 5 cm diameter NaI (Tl) crystal. To observe the detailed distribution of the ^{169}Yb–DTPA in the CSF high-resolution images were obtained using a gamma-camera (Nuclear Chicago HP).

Quantitative whole-body scans were carried out using a moving-couch system with two opposed 12·5 cm diameter crystals and digital readout (Trott *et al.*, 1973). Twenty-five-hole focusing collimators were used, giving a resolution (FWHM) of approximately 3 cm at the focus. The activities in the spinal subarachnoid space (SSS), intracranial subarachnoid space (ISS) and bladder were estimated by taking the total counts within the physical limits of the organ and expressing them as a percentage of the total body counts. This method was checked by using appropriate phantoms. The same geometrical areas were used on repeat measurements for each patient, so relative counts are accurate although the absolute values are estimated to be within only ± 15 per cent.

Blood samples were taken during the first 48 hours in most cases, and urine samples were obtained for the same period from one patient, together with a CSF sample at 48 hours.

Patients and Protocol

Seven patients with proven ALL and aged between 2 and 50 years have been treated, also one patient with acute myeloid leukaemia (AML) and one with diffuse histiocyctic lymphoma (DHL). The injection was carried out using standard lumbar puncture techniques with the body tilted slightly head down. The activities of the ^{90}Y–DTPA administered are shown in Table I. Two millicuries of ^{169}Yb–DTPA were administered together with the ^{90}Y–DTPA. Patients were encouraged to drink plenty of water for the first 48 hours to minimize the radiation dose to the bladder.

Case Reports

Case 1. Diagnosis: acute lymphatic leukaemia

A 23-year old male diagnosed in October 1971. Despite haematological remission, CNS relapse occurred in July 1972. He was treated with 2,500 rads in 18 days to the brain and with intrathecal methotrexate. A further CNS relapse occurred in March 1973 and an Omaya valve was constructed. As there was no response to intrathecal methotrexate, cytosine arabinoside was used with success. A third CNS relapse occurred in December 1973, and it was decided to give ^{90}Y–DTPA and craniospinal radiotherapy to maintain the CNS remission induced by intrathecal methotrexate (total 10 mg) and cytosine arabinoside (total 220 mg). There were no blast cells present during the ^{90}Y–DTPA treatment, but there was a further CNS relapse two months after completion.

Case 2. Diagnosis: acute lymphatic leukaemia

An 8-year-old boy diagnosed in May 1970 who was given prophylactic CNS radiotherapy (2,500 rads in 23 days to the brain and 2,400/20 to the spine) in November 1971. In July 1972 a bone marrow and CNS relapse was successfully treated by re-induction and intrathecal methotrexate. The same occurred in October 1973, and CNS blasts were again eliminated by intrathecal methotrexate. In April 1974 a further CNS relapse prompted the use of ^{90}Y–DTPA. A total of 8 mg methotrexate and 350 mg cytosine cleared the blasts before the intrathecal ^{90}Y–DTPA. He had a CNS relapse five and a half months after the completion of the ^{90}Y–DTPA therapy.

Case 3. Diagnosis: acute lymphatic leukaemia

A 21-year-old-man who at diagnosis in February 1974 was found to have leukaemia cells in the CSF and was treated with alternate intrathecal methotrexate and cytosine arabinoside. He was admitted in April 1974 with chemically-induced meningism. In June 1974 he had headache and CSF blasts were found. He was given alternate methotrexate (total 12 mg) and cytosine arabinoside (total 100 mg) followed by ^{90}Y–DTPA. There were no blasts at the time of the ^{90}Y–DTPA therapy, but he had a further CNS relapse the month after completion. All the injections were partially unsuccessful with whole-body retention at four hours of 45, 60 and 43 per cent of the dose, although the third injection was under radiological control after myodil had been successfully introduced.

Case 4. Diagnosis: acute lymphatic leukaemia

A 17-year-old youth, a Jehovah's witness, whose parents refused blood transfusions for him, diagnosed in December 1973, developed headaches and vomiting during remission induction. The CSF was clear of blasts, but methotrexate was instilled intrathecally. Prophylactic cranial irradiation was given in January 1974 (2,500 rads to the brain in three weeks) with intrathecal methotrexate. In February 1974 a lumbar puncture showed occasional blast cells in the CSF but further intrathecal methotrexate dispersed them. A further appearance of CSF blasts in May 1974 was controlled with cytosine arabinoside (total 300 mg) and ^{90}Y–DTPA and craniospinal radiotherapy were used to attempt to maintain the CNS remission. The patient remains well.

Case 5. Diagnosis: acute lymphatic leukaemia

A 48-year-old male, another Jehovah's witness, diagnosed in September 1973, also showed blasts in the CSF during remission induction. Initially he was treated with cranial radiotherapy and intrathecal methotrexate, but after severe nausea and vomiting, the radiotherapy was abandoned after approximately 300 rads and he was started on dexamethasone, but continued on methotrexate. The CSF was clear in December 1973, and he was maintained on bi-monthly methotrexate intrathecally. In August 1974 it was decided to use craniospinal irradiation, partially with external radiotherapy and partially with ^{90}Y–DTPA to spare the bone-marrow, in order to maintain the remission. There was CNS relapse three months after completion of the ^{90}Y therapy.

Case 6. Diagnosis: acute myeloid leukaemia

An 18-year-old girl, diagnosed in August 1973, who in July 1974 developed a right facial palsy and headaches. No response to intrathecal cytosine arabinoside (total 400 mg) led to a decision to use intrathecal methotrexate (total 24 mg) followed by ^{90}Y–DTPA. There were a few blasts (1/mm^3) at the start of the ^{90}Y–DTPA, however, both the first two injections were unsatisfactory and the CSF was clear at the third injection. The patient remains well.

Case 7. Diagnosis: acute lymphatic leukaemia

An 18-year-old youth who was diagnosed in November 1972, had prophylactic CNS radiation (2,500 rads in three weeks) in January and February 1973. A CNS relapse in January 1974 was treated with intrathecal methotrexate and cytosine arabinoside. In September 1974 he was well, but a high CSF blast count (371/mm^3) prompted the use of ^{90}Y–DTPA. 12 mg of intrathecal methotrexate was given the week before. At the time of the single injection of ^{90}Y–DTPA the blast count was 4/mm^3; a fortnight after it was 2/mm^3 and the patient continued on weekly methotrexate.

Case 8. Diagnosis: acute lymphatic leukaemia

A two-year-old baby diagnosed in May 1974. A neutropenic episode prevented prophylactic CNS irradiation in August 1974. Despite intrathecal methotrexate and cytosine arabinoside in September, he developed a CSF blast count of 45/mm^3, and it was decided to use ^{90}Y–DTPA. 35 mg of cytosine arabinoside was given intrathecally six and 15 days before the isotope therapy, and at the time of the ^{90}Y–DTPA injection the count was 1/mm^3. However, the blasts were not cleared and the patient continued on weekly methotrexate.

Case 9. Diagnosis: diffuse histiocytic lymphoma

A 43-year-old woman, diagnosed in December 1971, who developed papilloedema in October 1973 and later left optic atrophy. 3,360 rads (21 fractions in 27 days) were given to the whole brain with 4,130 rads to the left orbit (same fractionation). In October 1974 she was admitted with headaches and confusion. A lumbar puncture showed abnormal histiocyctes and she was treated with dexamethasone and intrathecal methotrexate (total 48 mg) without great success. An EMI brain scan showed no space-occupying lesion and intrathecal ^{90}Y-DTPA was given. The scintigram indicated a block at D1, only a small fraction of the isotope reaching the cistern. The whole-body retention at 18 hours was only 6 per cent. A subsequent diagnostic isotope cisternogram again indicated a partial block at D1; however, a myelogram showed no obstruction. We are unable to offer a satisfactory explanation. Malignant cells remained but cleared slowly with cytosine arabinoside.

RESULTS

Table II is a summary of the clinical results in terms of the effect of the ^{90}Y-DTPA therapy on the number of blast cells present in the CNS or on the length of remission after the treatment.

The intrathecal administration produced no complications. However, in 7 of the 23 administrations (Table I) only a fraction—in one case only a tenth—was retained in the CSF, the remainder either leaking from the puncture or being injected into the subdural space. This activity rapidly diffused into the ECF leading to a high blood level at 15 minutes and low whole-body retention at four hours. Apart from case 9 the isotope reached the basal cisterns by about 20 minutes, and circulated throughout the subarachnoid space during the subsequent few hours.

Figure 1 shows the whole-body, intracranial subarachnoid space (ISS) and spinal subarachnoid space (SSS) retention for one typical administration. The whole-body retention measured by the external counter agrees within 5 per cent with the retention derived from the urine data. A CSF sample at 48 hours gave 0·017 per cent, dose per ml. and assuming 90 ml. of CSF in the SSS (see dosimetry section) this gives 1·5 per cent of the dose in the SSS compared with 0·8 per cent from whole body scanning.

Blood samples gave a low initial radioactive concentration rising to a maximum at 10–15 hours. If the plasma concentration is multiplied by the compartment size for DTPA, taken in this case to be 16 litres, then the total activity within the ECF is obtained (Fig. 1).

Table III shows, for one patient, the total activity in various organs at 4·5, 24 and 49 hours, taking the data from Fig. 1 together with retention in the bladder from whole body scanning—the patient did not urinate between the scan and whole-body count. The kidney uptake was estimated assuming a transit time of 4 minutes and GFR of 120 ml./minute.

TABLE I

Patient	Date	^{90}Y-DTPA given	Surface doses received by brain	Surface doses received by spinal cord
		mCi	rads	rads
1	22.1.74	1·0	235	73
	11.2.74	1·6	362	96
	4.3.74	2·9	543	123
	11.3.74	2·7	429	139
	18.3.74	3·8	657	181
		12·0	2226	612
2	15.5.74	1·9	618†	161†
	29.5.74	2·0	650†	170†
	10.6.74	2·1	683†	179†
		6·0	1,951	510
	22.5.74 -29.5.74	External	900	877
3	22.7.74	3·8*	386	91
	5.8.74	4·9*	< 100	< 100
	19.8.74	4·5*	< 100	< 100
	31.7.74 -7.8.74	External	1,000	1,000
4	5.8.74	4·3	1,051	353
	19.8.74	3·9	657	186
	2.9.74	7·5	1,525	432
			3,233	971
	10.8.74 -18.8.74	External	1,000	1,000
5	6.8.74	3·2*	302	142
	20.8.74	5·2	955	306
	3.9.74	8·7	1,384	462
			2,641	910
	12.8.74 -19.8.74	External	1,000	1,000
6	20.8.74	4·4*	372	107
	30.8.74	8·5*	243	110
	2.9.74	6·1	1,165	378
			1,780	595
7	13.9.74	8·1	2,182	280
8	26.9.74	1·0	1,084†	244†
9	24.10.74	9·9*	< 100	< 100

*Unsatisfactory injection. See text.
†Very limited data available for calculation. Estimates.

Table IV shows the mean and range of whole body, ISS and SSS retention at 24 and 48 hours for all administrations, excluding those where the injection was unsatisfactory.

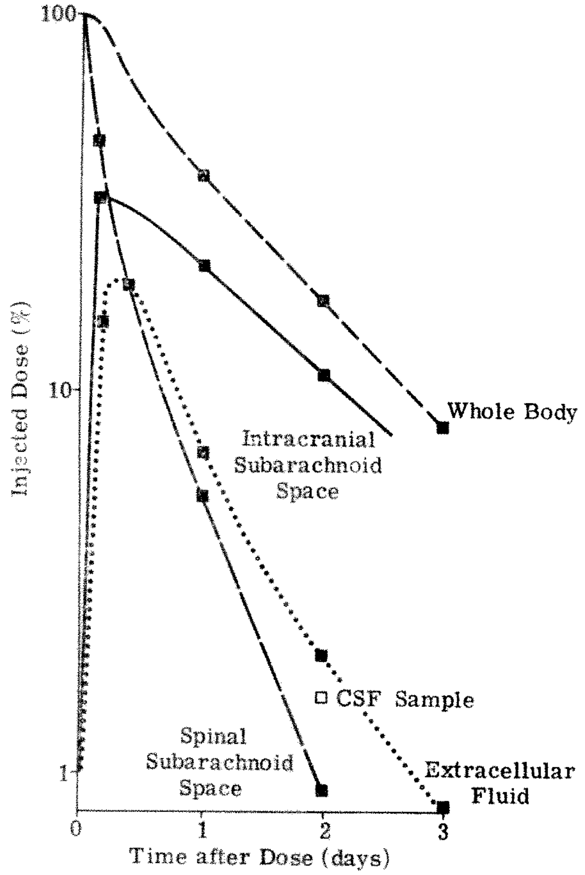

Fig. 1.

Whole body, intracranial and spinal subarachnoid space and extracellular fluid retention of ^{169}Yb–DTPA in one patient (Case 1) after intrathecal administration of 1·0 mCi ^{90}Y–DTPA and 2·0 mCi ^{169}Yb–DTPA.

TABLE II
Clinical Results

Case no.	No. of CNS relapses prior to ^{90}Y–DTPA therapy	CNS Situation at time of ^{90}Y–DTPA therapy	CNS results of ^{90}Y–DTPA therapy
1	Three	Remission	Relapse two months later
2	Three	Remission	Relapse five and a half months later
3	Two	Remission	Unassessable
4	Two	Remission	Still in remission at nine months
5	One	Remission	Relapse three months later
6	One	One blast/mm^3	Still in remission at six months
7	Three	Four blasts/mm^3	Blasts not cleared
8	One	One blast/mm^3	Blast not cleared
9	Two	Abnormal histiocytes present	Unassessable

TABLE III
Organ retention after intrathecal injection

	% administered dose		
	4·5 h	24 h	49 h
Whole body retention	96	38	18
Intracranial subarachnoid space	31·4	22·4	11·6
Spinal subarachnoid space	40·7	5·8	0·8
Extra cellular fluid	13·4	7·6	1·9
Kidney	0·5	0·2	—
Bladder	4·8	1·3	1·7
	90·8	37·3	15·0

Data from one administration (see text for details)

A significant long-term retention of the ^{169}Yb–DTPA was observed. This was found to be between 3 and 8 per cent at one week and 1 and 3 per cent at two months.

Dosimetry

To calculate the radiation dose to the surfaces in contact with the CSF, knowledge of the accumulated activity in μCi–h for each part of the CSF is required, together with information on the target source geometry and thickness of the source.

The uptake and retention data for the CSF has been divided into two parts; that for the intracranial subarachnoid space and that for the spinal subarachnoid space. It has not been considered that a more detailed division is justified by the other data available. The accumulated activity was obtained by integrating the area underneath the activity-time curve.

The volume of the CSF and its division amongst the various components of the subarachnoid space is not easily obtained for individual patients and values of 90 cm^3 for the SSS and 40 cm^3 for the ICS have been taken for adults (Lups and Haan, 1954; Lindgren, 1939 and Di Chiro and Fisher, 1964; Peterson and Kieffer, 1968). The total volume for Case 2 (eight years old) was taken as 80 cm^3 and for

TABLE IV

WHOLE BODY, INTRACRANIAL SUBARACHNOID SPACE AND SPINAL SUBARACHNOID SPACE RETENTION

		% administered dose		
		24 h	48 h	Administrations
Whole body	Range	50–35	20–12	15
	Mean	40	16	14
ISS	Range	30–15	12–6	12
	Mean	22	9	11
SSS	Range	9–2	2–0·8	12
	Mean	5·3	1·2	11

TABLE V

ABSORBED DOSE ESTIMATE FROM INTRATHECALLY ADMINISTERED ^{90}Y AND ^{169}Yb (rad/mCi administered)

	^{90}Y	^{169}Yb
Brain (surface)	205	38
Spinal cord (surface)	120	20
Nerve root	240	40
Kidney	0·5	0·3
Bladder	10	1·6
Whole body	1·0	0·2

Case 8 (two years old) as 50 cm^3 (Lups and Haan, 1954). However, the volume for the intracranial space includes the ventricles, which probably account for half the volume, but the ^{90}Y–DTPA does not diffuse into the ventricular space to any large extent, as demonstrated by the scintigrams.

The surface doses have been calculated for the ^{90}Y by assuming a dose of half that within an infinite source at the same concentration. This is a simplification and account needs to be taken of the target-source geometry and of the fact that the range of the ^{90}Y β particles is similar to the thickness of the cylindrical sheath of liquid around the spinal cord (Hilditch, 1968; Johnston *et al.*, 1971, Harbert *et al.*, 1970, Beatty, 1973). For ^{90}Y the percentage reduction of the surface dose for a typical thickness of the cylindrical sheath of CSF around the spinal cord of 0·35 cm (Hilditch, 1968) as compared with that of an infinite slab of infinite thickness, is approximately ten (Loevinger, Japha and Brownell, 1956). This reduction factor takes into account only the thickness of the source, and assumes a plane rather than a curved source geometry. The cylindrical sheath geometry of the CSF around the spinal cord will increase the radiation dose to the surface of the spinal cord compared to the planar situation; the smaller the radius the higher the absorbed dose. Thus the two effects, that of the finite thickness of the source and that due to curvature of the source, are opposite for the spinal cord and partially cancel each other. The two effects will have different magnitudes throughout the subarachnoid space and the surface doses stated have not allowed for either effect. The errors due to other factors, such as uncertainty in the detailed distribution and concentration of the isotope are probably larger.

Table I gives the estimated surface dose to the brain and spinal cord for all the patients treated.

Table V gives the data for the average absorbed dose per mCi successfully administered. The nerve root is assumed to be infinitely thin. Thus the absorbed dose will be equal to that at a point in an infinite source, and no account has been taken of the non-uniform mixing in the intracranial CSF. The dose to the bladder was derived from the one patient on whom urine measurements were made.

The ^{169}Yb absorbed doses (Table V) do not take into account the long-term retention. The calculations have been carried out in a similar fashion to those for the ^{90}Y, taking the absorbed surfaces dose due to non-penetrating radiation as half that within an infinite source at the same concentration. The effects due to the thickness and geometry of the source are negligible when considering the dose to the surface of the cord. However, because of the very low energy of the electrons, most of the electrons will be absorbed in a thin layer; the dose at a depth of 0·1 mm due to the electrons is less than 1 per cent of the surface dose. At the surface of the cord, the dose due to the penetrating radiation is about 5 per cent of that due to the non-penetrating radiation (Morin and Brookeman, 1974).

DISCUSSION

Several groups of workers have reported the use of intrathecal radioactive gold colloid, mainly to treat secondaries from brain tumours (Kerr, Schwartz and Seaman, 1954; Rieselbach *et al.*, 1962; D'Angio *et al.*, 1968; Gold *et al.*, 1970). However, it is difficult to obtain a uniform distribution of the gold and there is the danger of loculation. The gold also usually causes meningeal irritation. ^{131}I-labelled human serum albumin was also considered for intrathecal therapy but was rejected as the compound when injected intrathecally is de-iodinated *in vivo* and free iodide released. Even with the thyroid blocked this can lead to a higher dose to the thyroid than to the spinal cord (Johnston *et al.*, 1971).

^{90}Y was chosen as it has a high β energy, thereby obtaining a clinically significant radiation dose at

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1–2 mm depth; the 50 per cent depth dose for ^{90}Y under the conditions considered is about 0·1 cm (Loevinger *et al.*, 1956; Beatty, 1973).

It has also a fairly short half-life, thus minimizing the danger due to any long-term retention of the radiopharmaceutical. It chelates easily with DTPA and has a high stability constant ($\log k > 18$).

The long-term retention of ^{169}Yb–DTPA has been noted by several authors (Barbizet, *et al.*, 1972; Morin and De Land, 1974; Alazraki *et al.*, 1974) however, the reason for the retention is not understood.

The dosimetry shows that therapeutic size doses of radiation can be delivered to the CSF and meningeal surfaces in contact with the CSF with a low radiation dose to other organs. However, faster clearance from the subarachnoid space compared with the intracranial CSF is a major disadvantage as it leads to large variations in absorbed dose within the CSF and to the meningeal surfaces (Table I).

The problem of extravasation into the epidural space and surrounding tissue has been encountered in 48 per cent of cases by Mahaley *et al.* (1974); McCullough *et al.* (1972) and Kieffer *et al.* (1971) have also noted this problem.

The present technique has been shown, for the 23 administrations carried out to date, to be safe and to have no undesirable side effects.

The first six patients were treated when in remission and received multiple intrathecal administrations of ^{90}Y. In three patients external beam therapy of not more than 1,000 rads to the brain and spinal cord was also given. The clinical results in these cases were not encouraging as three out of five assessable cases relapsed within six months. It was therefore decided to test the effects of larger single administrations on the blast cell count. In view of the failure to clear the blasts in both evaluable cases we have abandoned the use of intrathecal ^{90}Y–DTPA at these doses.

Although the present agent has been shown to be unsatisfactory with the doses administered, work is being carried out to find a more suitable agent with a longer and more uniform biological half-life in the CSF, but with the same desirable lack of organ uptake outside the CSF and as rapid excretion from the body as DTPA.

Acknowledgments

All the patients in this study were under the care of Dr. T. J. McElwain and we would like to thank him for his advice and co-operation.

We gratefully acknowledge the Radiochemical Centre for co-operation and the supply of the radiopharmaceuticals. We would also like to thank Dr. V. R. McCready and the staff of the Department of Nuclear Medicine for their help, and in carrying out some of the measurements, and Dr. N. G. Trott for advice and encouragement.

REFERENCES

Alazraki, N., Hurwitz, S., Halpern, W. E., and Ashburn, W. L., 1974. ^{169}Yb-DTPA Cisternography: How many rads does the brain receive? *Journal of Nuclear Medicine, 15*, 643.

Aur, R. J. A., Simone, J. V., Hustu, H. O., and Verzosa, M. S., 1972. A comparative study of central nervous system irradiation and intensive chemotherapy early in remission of childhood acute lymphocytic leukemia. *Cancer, 29*, 381–391.

Barbizet, J., Thomas, J., Galle, P., Moretti, J.-L., and Pitton, R., 1972. La cisternographie et la ventriculographie isotopiques. *La Nouvelle Presse medicale, 1*, 2899–2901.

Beatty, H. E., 1973. Dosimetric studies of the radiotherapy of the central nervous system. M.Sc. thesis, University of London.

D'Angio, G. J., French, L. A., Stadlan, E. M., and Kieffer, S. A., 1968. Intrathecal radioisotopes for the treatment of brain tumours. *Clinical Neurosurgery, 15*, 288–300.

Di Chiro, G., and Fisher, R. L., 1964. Contrast radiography of the spinal cord. *Archives of Neurology, 11*, 125–142.

Gold, L. H. A., Kieffer, S. A., D'Angio, G. J., Fallon, V. T., and Long, D. M., 1970. Current status of intrathecal radiogold in the treatment of medulloblastoma. *9th Symposium Neuroradiologicum, Gothenburg*, 329–340.

Harbert, J. C., and McCullough, D. C., 1970. Spinal cord dosimetry in ^{131}I-IHSA Cisternography. *Journal of Nuclear Medicine, 11*, 534–541.

Hustu, H. O., Aur, R. J. A., Verzosa, M. S., Simone, J. V., and Pinkell, D., 1973. Prevention of central nervous system leukemia by irradiation. *Cancer, 32*, 585–597.

Hilditch, T. E., 1968. Radiation dose in isotope encephalography. *Lancet, 2*, 573–574.

Johnston, R., Staab, E. V., Brill, A. N., and Allen, J. H., 1971. Radiation dosimetry associated with the intrathecal administration of ^{131}I human serum albumin. *British Journal of Radiology, 45*, 444–451.

Kerr, F. W. L., Schwartz, H. G., and Seaman, W. B., 1954. Experimental effects of radioactive colloidal gold in the subarachnoid space. *American Medical Association Archives of Surgery, 69*, 694–706.

Kieffer, S. A., Wolfe, J. M., Prentice, W. B., and Loken, M. K., 1971. Scinticisternography in individuals without known neurological disease. *American Journal of Roentgenology, 112*, 225–236.

Kovach, A., 1973. A method for the determination of radiochemical purity of ^{169}Yb-DTPA. In *New Developments in Radiopharmaceuticals and labelled compounds*, pp.145–150 (IAEA, Vienna).

Lindgren, E., 1939. Myelographie mit luft. *Nervenarzt. 12*, 57–61.

Loevinger, R., Japha, E. M., and Brownell, G. L., 1956. *Discrete Radioisotope Sources in Radiation Dosimetry*, Ed. G. J. Hine and G. L. Brownell.

Lups, S. and Haan, H., 1954. *The Cerebrospinal Fluid* (Elsevier, Amsterdam).

Mahaley, M. S., Wilkinson, R. H., Sivalingham, S., Friedman, H., Tyson, W., and Goodrich, J. K., 1974. Radionuclide blood levels during cisternography of patients with normal pressure hydrocephalus or Alzheimer's disease. *Journal of Neurosurgery, 41*, 471–480.

McCullough, D. C., Harbert, J. C., Miale, A., Landis, G. A., and De Blanc, H. J., 1972. Radioisotope cisternography in the evaluation of hydrocephalus in infancy and childhood. *Radiology, 102*, 645–652.

Morin, R. L., and DeLand, F. H., 1974. Safety of ^{169}Yb–DTPA in Cisternography. *Journal of Nuclear Medicine, 15*, 375–376.

MORIN, R. L., and BROOKEMAN, V. A., 1974. ^{169}Yb-DTPA distribution and dosimetry in cisternography. *Journal of Nuclear Medicine, 15*, 786–796.

PETERSON, H. O., and KIEFFER, S. W., 1968. Large volume pantopaque myelography: evaluation of nearly 1,000 cases. *69th Annual Meeting Roentgen Ray Society, New Orleans.*

RIESELBACH, R. E., DI CHIRO, G., FREIREICH, E. J., and RALL, D. P. 1962. Subarachnoid distribution of drugs after lumbar injection. *New England Journal of Medicine, 267*, 1273–1278.

TROTT, M. G., COTTRALL, M. F., WELLS, P. G., and McCready, V. R. 1973. *Investigations of sequential distribution using a low-background whole body scanner with digital output. Medical Radioisotopes Scintigraphy, 1972*, pp. 61–78. (IAEA, Vienna).

WAGNER, H. N., HOSAIN, F., DE LAND, F. H., and SOM, P., 1970. A new radiopharmaceutical for cisternography. *Radiology, 95*, 121–125.

WILLOUGHBY, M. L. N., 1974. Treatment of overt meningeal leukaemia. *Lancet, 1*, 363.

Book review

Supplement on Cancer to the Registrar General's Statistical Review of England and Wales for the Years 1968–1970. 1975 (H.M.S.O.), £5·20.

The conventional type of book review is inappropriate for a publication of this kind, and it seems most useful to quote the summary provided inside each volume, by the authors.

This volume analyses:

(a) cancer cases first diagnosed in 1968, in 1969 and in 1970,

(b) the rate of survival over 15 years of cancer cases first registered in 1954 and 1955, and

(c) the five-year rate of survival of cancer cases registered in 1962 and 1963.

The main tables in this volume are similar to those of earlier volumes and show numbers of registrations and registration rates by site, sex and age, distinguishing urban and rural aggregates for England and Wales and analysing them by site and sex for hospital region of residence.

The national cancer registration scheme provides for Regional Registries to submit a standard abstract card to the Office of Population Censuses and Surveys for each cancer case diagnosed (in hospital) within their respective areas. Because the scheme is voluntary, its coverage of registration varies from region to region. Nevertheless, these defects of reporting are not thought to be great enough to invalidate the main statistics (especially the long-term survival rate), and in what follows the reported rates are treated as if they were the actual rates, and a cancer is taken to mean a category of cancer as classified in the usual way (ICD 8th Revision) by site.

The tables show that the incidence of most cancers per head is greater in urban than in rural areas. The stronger urban/rural gradient for males is due to the large contribution from lung cancer. There are more types of cancer where the rate of incidence is increasing than where it is decreasing. Notable among the former group are cancer of oesophagus, pancreas, lung (especially in women), ovary, testis, bladder and multiple myeloma. The incidence of cancer of lip, tongue and stomach are all decreasing. There are some regional variations in cancer incidence. Of the most common cancers, cancer of the stomach is most frequent in the Newcastle region and Wales, and least frequent in the south and east of the country. Lung cancer is most common in the four Metropolitan and Liverpool regions, least common in Wales and the relatively rural regions of East Anglia and the South West. Breast cancer is less common in the Newcastle and Liverpool regions but there are no regions of notably high incidence.

Tables show survivorship at five and 15 years of patients with cancer in different sites. The 15-year survival tables are the first produced on a national basis. By examining the survival rates between five and 15 years after diagnosis it is possible to infer the proportion of cancers cured. In the diagrams two survival curves are shown for each year: one shows the crude survival rate and the other is corrected by allowing for the deaths which would be expected to occur from other causes. The effect of this correction would be to show 100 per cent survival if the cancer concerned had no lethal effect or was always cured. The line on the graph would become horizonal; it follows that the slope of the corrected survival curve indicates the curability of the cancer; a steep slope indicates that cancer mortality is high (*e.g.* in the first five years); a shallow slope indicates that cancer mortality is moderate (*e.g.* from the sixth year on). A horizontal curve indicates that there is no longer any excess mortality due to cancer. An upward curve (rarely seen) suggests that the persons with this cancer are less likely to die than are a random sample of people of the same age and sex, possibly because the cancer occurs more among otherwise relatively healthy groups of persons such as, for example, happens with skin cancer among farmers.

I would simply like to add that one must be impressed by the great effort involved in producing these figures and I found the section on explanatory notes very helpful. This is rather more than the title at first suggests and is in itself quite informative for those not fully acquainted with statistical methods.

It is also useful to know that the Cancer Registration Section of the Office of Population Censuses and Surveys invites users of the material to communicate with them about points of interest. This facility might not have been realized by all of our readers.

B. T. HALE.

1976, *British Journal of Radiology*, *49*, 148–150

Bowel gas—a cause of elevated dose in radiotherapy

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(*Received November, 1974*)

ABSTRACT

The presence of gas in bowel could lead to higher than expected doses being given in the radiotherapy of abdominal and pelvic tumours. Radiation detectors were placed in the uterus and vagina of ten patients with carcinoma of cervix, and the actual dose compared with that expected when anterior fields of treatment were employed. Elevations greater than 10 per cent were obtained in six, and severe post-radiation morbidity subsequently occurred in two of the three showing the highest readings.

In planning radiotherapy using high-energy radiation to the pelvis and abdomen, it is customary to assume uniform absorption through all tissues. Since 1966, we have employed lateral radiographs with markers on the anterior and posterior skin surfaces in order to help determine the volume for treatment (Collins and Blake, 1968). In many of the patients so radiographed, a considerable amount of gas in small and large bowel could be seen (Fig. 1). It was calculated that such gas could lead to higher than expected doses due to increased transmission. If the gas in the small and large intestine were equivalent to a belt 2·5 cm in thickness, then this would result in an elevation of dose in the anterior part of the treatment volume in the pelvis of approximately 10 per cent (Batho, 1964; Young and Gaylord, 1970). When the planned tumour dose is considered to be the maximum tolerable to normal tissues, such an elevation must increase the incidence of morbidity.

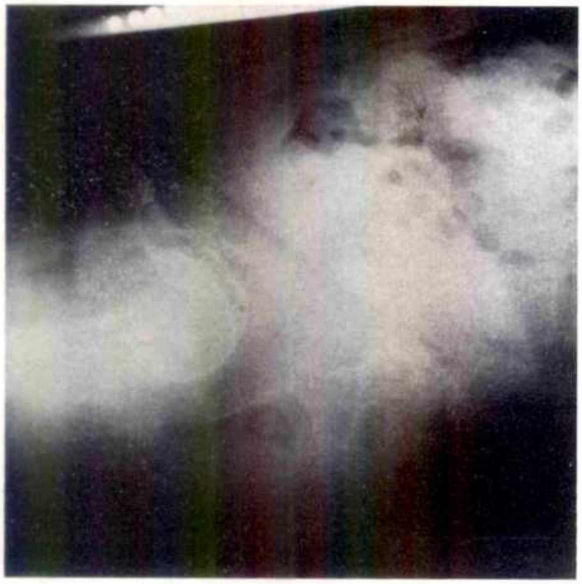

FIG. 1.

A lateral radiograph of the pelvis taken for planning of radiotherapy to carcinoma of the cervix.

Ryall and Rapley (1969) have measured the dose in the rectum and recto-sigmoid in patients undergoing pelvic irradiation, and have reported measured doses to be greater than those planned. They suggested that air spaces may be a source of error in pelvic dosimetry.

To investigate this possibility we have placed radiation detectors in the uterus, and have compared actual with expected doses. Immediate and late effects of radiotherapy upon the bowel have been observed in these patients. Early work using ionization chambers suggested that the dose recorded when an anterior field was used was greater than expected but the technique was found to be technically unsatisfactory. The use of lithium fluoride rods has led to more consistent results.

All patients with carcinoma of cervix are assessed by examination under anaesthesia prior to treatment (Dische, 1974). In a number of patients at the conclusion of the examination a polythene tube, 25 cm long and 0·6 cm external diameter, sealed at the distant end, was introduced to the uterus and held in place by some packing in the vagina. A catheter was introduced into the bladder and urine allowed to drain continuously.

Later in the day, an inner catheter containing lead markers was introduced into the polythene tube and radiographs taken with skin markers in order to locate the catheter. This was replaced by a second inner catheter containing lithium fluoride rods in groups of five separated by pieces of lead (Fig. 2). The rods were 1 mm in diameter and 6 mm long (Teledyne-Isotopes Mr-Lif-7 microrods). A standard annealing procedure was used, *viz.*—400°C. for one hour, followed by 80°C for 24 hours (Cameron *et al.*, 1961). An anterior treatment field was set up using a cobalt unit operating at 90 cm FSD and a standard dose of 10 rads at 4 mm below the skin employed.

The exact position of the groups of lithium fluoride rods was marked on an outline of the patient, and the expected dose calculated from standard

TABLE I

Patient No.	Stage	Actual doses expressed as a ratio—actual/expected	Impression of bowel gas in radiographs	Morbidity of radiotherapy		Follow-up
				During treatment	Late changes	
1	3	1·11	0	Moderate	None	Dead at 19 months due to distant metastases
2	2A	1·11	+	Moderate	Occasional rectal bleeding	Well, free of tumour at 31 months
3	1B	1·00	0	None	None	Alive at 31 months but with pulmonary metastases
4	2A	1·00 1·00	+	Slight	None	Dead due to distant metastases at 18 months
5	2A	1·00 1·10	+	None	None	Well, free of tumour at 31 months
6	3	1·33 1·22	++	Moderate	Marked radiation change in pelvis and bowel	Dead at 11 months with distant metastases; pelvic abscess probably due to radiation change in bowel
7	1B*	1·10 1·17 1·22	++	Moderate	One episode of haematuria No bowel morbidity	Well, free of tumour at 26 months
8	3	1·10 1·09 1·12	0	Slight	Occasional rectal bleeding	Well, free of tumour at 21 months
9	2A	1·25 1·00	++	Moderate	None	Dead at 17 months due to local recurrence and distant metastases
10	3	1·25	++	Slight	Died after necrosis of upper rectum	Dead at 13 months. At post-mortem, no tumour in pelvis but secondary deposits in para-aortic nodes

*At 'Wertheim' hysterectomy, after pre-operative radium, a large secondary node was found on the pelvic wall and post operative radiotherapy given to pelvis.
The doses actually obtained are compared with those expected for homogeneous absorption using depth dose data and expressed as a ratio—actual dose to that expected. Where there were two or three groups of lithium fluoride rods the results in those highest in the uterus are shown on the left. Bowel reactions during treatment and late effects are also noted.

depth-dose data. The doses received by the lithium fluoride rods were read 24 hours after exposure to allow for decay of low temperature peaks. Calibration of the rods used was performed by ^{60}Co irradiation of identical rods alongside a Baldwin-Farmer substandard ionization monitor under full build-up conditions. The calibration rods were used to set the controls of the readout instrument (Teledyne isotopes type 7100 TS) so as to give a reasonable number of digits/R (usually 20–25). The test rods were then read out. The average standard deviation for groups of five test rods was $\pm 3{\cdot}5$ per cent.

A series of ten patients was studied between February 1972 and April 1973 and these patients have been followed since radiotherapy was completed. All received whole pelvis irradiation and a single application of radium (Dische, 1974). The standard régime consisted of 5,500 R minimum tumour dose in 27 fractions over five and a half weeks, followed by a radium application to give 1,800 R at Point A.

The table summarizes the results obtained. The number of groups of lithium-fluoride rods within the treatment field varied from case to case according to the length of the uterus and the vagina. Only those groups of rods which were well within the treatment field are included. The results are shown as a ratio—the actual dose to that expected for

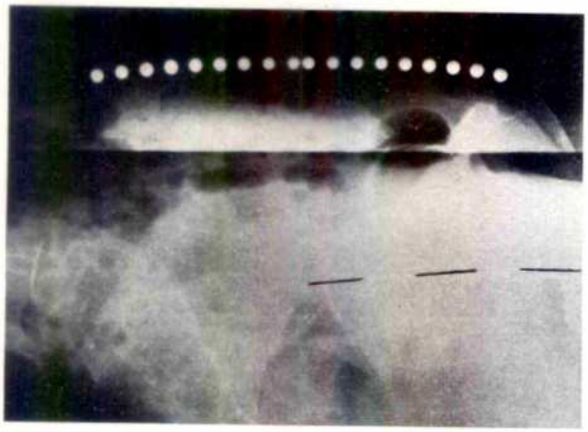

FIG. 2.

A lateral radiograph with skin markers taken to relate the uterine tube, which will contain the lithium fluoride rods, to the surface of the abdomen.

homogeneous absorption using the depth-dose data. Where there were two or three readings, the one highest in the uterus is given on the left. Bowel reactions during treatment and late effects are shown. In six of ten patients actual doses were recorded which were 10 per cent or more above those expected. The highest reading was obtained in Patient 10, who subsequently died due to radiation changes in the recto-sigmoid without recurrence of tumour. High readings were also obtained in Patients 6 and 7; of these two, Patient 7 died due to metastatic tumour without recurrence in the treated area, but there were considerable symptoms due to radiation effects in the bowel before death and a pelvic abscess, probably due to radiation necrosis in the bowel wall, was seen at post-mortem.

The techniques of treatment used in these patients were two, three or four field arrangements, the choice depending on patient size. Posterior and postero-lateral fields are not so likely to be affected by bowel gas as anterior fields, and there is the possibility of a reduction of dose due to increased absorption in bone. Attempts were made to measure doses using such fields but difficulties in exactly locating the position of catheters relative to the surface were much greater and consistent results were difficult to achieve. The increase of dosage recorded using anterior fields probably exaggerates the true elevation of dose actually received in these patients where multiple fields were employed. Nevertheless, the results indicate that the presence of bowel gas does elevate the dosage achieved in the treatment volume. These observations are supported by the findings of post-radiation damage in two of the three cases showing the highest readings.

A more satisfactory technique of demonstrating the effect of bowel gas has been developed using transmission measurements according to the method originally described by Burlin (1957), when working in this centre, for evaluating the dose to the thorax in rotational ^{60}Co therapy. This technique can be used for repeated observations through a course of radiotherapy. Methods to overcome the problem of inhomogeneity due to bowel gas are being assessed.

REFERENCES

BATHO, H. F., 1964. Lung corrections in cobalt 60 beam therapy. *Journal of the Canadian Association of Radiologists*, *15*, 79–83.

BURLIN, T. E., 1957. The elevation of the dose to the thorax in rotational cobalt 60 therapy. *British Journal of Radiology*, *30*, 543–549.

CAMERON, J. R., DANIELS, F., JOHNSON, N., and KENNEY, G., 1961. Radiation dosimetry utilizing the thermoluminescence of lithium fluoride. *Science*, *134*, 333–334.

COLLINS, V., and BLAKE, K. C., 1968. Relationship of skin surface to tumour volume. *Radiography*, *34*, 204–206.

DISCHE, S., 1974. The hyperbaric oxygen chamber in the radiotheraphy of carcinoma of the uterine cervix. *British Journal of Radiology*, *47*, 99–107.

RYALL, R. D. H., and RAPLEY, L. F., 1969. A source of error in pelvic dosimetry. *South African Medical Journal*, *43*, 1493–1495.

YOUNG, E. M., and GAYLORD, J. D., 1970. Experimental tests of corrections for tissue inhomogeneities in radiotherapy. *British Journal of Radiology*, *43*, 349–355.

Book review

The Radiology of Joint Disease. By D. M. Forrester and J. W. Nesson, pp. 474, 1973 (Philadelphia, London and Toronto, W. B. Saunders and Company), £9·60.

This book is one of a series of monographs in clinical radiology, and presents a systematic radiological approach to the analysis of arthropathy. Starting from fundamental principles, the authors set out to educate the reader in a most entertaining and refreshing manner. While some readers might prefer a more formal style, I feel that the authors deserve much congratulation for scoring such a notable success with this form of presentation.

Following a general introductory section, the radiological appearances peculiar to individual joints are then considered in detail. To emphasize the importance of radiological hallmark signs, the reader is presented with a series of challenging problems after each chapter. The quality of radiographic illustration is a particularly outstanding feature. Without exception, each abnormality is revealed in the clearest detail. Frequent use is made of histological slab sections to illustrate the pathological basis for the radiological changes.

Radiographic information and facts are presented in a form which is directly applicable to practical problem solving. Although one must take issue with the statement that unilateral sacro-iliitis excludes ankylosing spondylitis, this is but a small and trifling scab amidst such a cornucopia. This book is warmly commended not for the library shelf, but for the bedside!

W. M. PARK.

1976, *British Journal of Radiology*, *49*, 151–155

Prediction of human spleen size by computer analysis of splenic scintigrams

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ABSTRACT

A method of assessing spleen size from splenic scintigraphs obtained using autologous heat damaged ^{99}Tc^{m}-labelled red cells is described. The method depends on a "computed volume" estimate. The method has a correlation coefficient of 0·989 with the exsanguinated weight of the spleen after splenectomy and has been shown to have an accuracy superior to methods previously described.

The involvement of the spleen in human disease is poorly understood and descriptions of changes in the spleen are usually based on those found in morbid anatomical or surgical specimens. Dynamic changes in specific functions such as red-cell destruction can be observed but probably reflect red-cell abnormalities rather than changes in the spleen. In many disease states there is a need to be able to monitor changes, especially in spleen size, in relation to the course of the disease. Changes in spleen size in animals have been reported in association with immunological phenomena (Congdon and Makinodan, 1961; Old *et al.*, 1961; Simonsen, 1961). Accurate monitoring of spleen size in man would allow observations of dynamic changes in relation to an immunological stimulus or in diseases which may have an immunological component.

Clinical examination can monitor changes in truly massive splenomegaly but in general, spleens have to be larger than 750 g before half of them are palpated (Fischer and Leon, 1969). To detect lesser degrees of splenic enlargement an alternative method is required. Unfortunately, invariably many methods do not demonstrate the spleen. Radiography is successful in only 17 per cent of abdominal films (Rosenbaum, Leiber and Pellegrino, 1964) and although gas insufflation into the gastrointestinal tract or peritoneum can improve on this, invariably the spleen is not demonstrated (Zelman, 1958; Rosch, 1965). Radiographs taken at specific times during intravenous pyelography or coeliac arteriography (which is not without risk) can demonstrate the spleen so that its size can be assessed (Blendis, Williams and Kreel, 1969). However, Blendis made no comment as to the certainty with which the spleen could be demonstrated and the size was calculated from a single two-dimensional image of the organ.

Radioisotopic methods almost invariably demonstrate the spleen long enough for detailed analysis of multiple images of the organ (Sigel, Becker and Hurley, 1970). Radioactively-labelled colloids which are commonly used, are removed by reticulo-endothelial cells in the liver and spleen and provide images of both organs. Liver and spleen images give the most useful information in the clinical situation but the intensity of the liver image can make detailed study of the spleen difficult (McIntyre and Wagner, 1970) and the effect is compounded when the spleen is greatly enlarged (Westin *et al.*, 1972). Images of the spleen alone, allowing detailed analysis of a number of views of the organ, can only be obtained using labelled damaged red cells, although careful control of the degree of red-cell damage is necessary to ensure a purely splenic image (McIntyre, 1972).

It is the purpose of this paper to report the use of a computer method of assessing organ size in man. The method of calculating volume has been previously described and shown to be valid in phantom and animal experiments (Leach *et al.*, 1975). This method has been used to assess spleen size in man from splenic scintigraphs obtained using autologous heat damaged ^{99}Tc^{m}-labelled red cells.

METHODS

Red-cell labelling

Autologous heat-damaged technetium-labelled red cells are prepared using a method similar to that of McRae and Valk (1972). Special care is taken to ensure an aseptic technique. Washing of the erythrocytes prior to heating should remove all traces of plasma and at all stages erythrocytes are handled with care, because of the increased fragility after heating. Care is also taken to prevent oxidation of the reducing agent, stannous chloride, used to fix the technetium label, and therefore fresh preparations are used. This method usually provides satisfactory concentration of damaged cells in the spleen and there has been only minimal interference from activity in the liver or bloodstream.

The amount of tin used gives an immediate local blood concentration of approximately 0·5 μg/ml.

which is approximately twice the mean blood tin concentration reported in normal human subjects (Hamilton, 1971). Toxic effects are often detectable in animals when the total body burden approaches 350 mg./kg (Fischer, 1957). The amount transfused with the label is approximately 4×10^{-6} of this amount.

Scintigraphy

Scintigraphy was commenced 20 minutes after reinjection of the labelled red cells using a Nuclear Chicago PHO Gamma III gamma-camera. Counts were acquired in the multichannel analyser memory of a Nuclear Data 50:50 data analysis system. This memory comprises a 64×64 array and counts were accumulated until the maximum channel content was approximately 1,000. The memory contents were then recorded on magnetic tape. With the patient in the supine position, anterior, posterior and lateral images of the spleen were obtained by rotating the camera. All calculations were carried out with the aid of a PDP 8/L computer interfaced with the multichannel analyser using for the most part, standard programs supplied by Nuclear Data.

Calculations

Computerized volume calculation. The computer calculation of volume described by Leach *et al.*, (1975) was used. This method employs the 25 per cent count contour to define the "edge" of the organ on the scintigraph and is based on phantom and animal experiments. Uniform activity throughout the spleen is assumed and the total count within the 25 per cent count contour is taken to reflect the total volume of the spleen (Clarke *et al.*, 1972). The count in the analyser channel containing the maximum content is designated the "maximum count". The maximum count reflects the greatest thickness of the organ at right-angles to the plane of the scintigraph and this thickness can be measured from a second scintigraph at right-angles to the first. Because of the shape and positioning of the spleen within the abdominal cavity, a lateral oblique view should be used to ascertain the true thickness and the views at right-angles employed to obtain the total count. Practical realities in positioning the patient have resulted in the anterior and posterior views being used to give the sum of the counts and the maximum count and the lateral view has been used to estimate the thickness. To minimize the effects of absorption the anterior and posterior counts are added to give both the sum counts and the maximum count. The area represented by a single channel in the analyser can be determined by reference to a standard line source and is designated "unit matrix area". The "unit matrix area" and the thickness at the maximum count (in unit matrix lengths) allow the volume represented by the maximum count to be calculated. Dividing the maximum count by this calculated volume gives an estimate (in terms of counts) of a "unit matrix volume" of splenic tissue. The total splenic volume in matrix units is obtained by dividing the total count within the 25 per cent count contour by the count content of a unit matrix volume of splenic tissue (Fig. 1). This can be changed to metric units by reference to the line source measurements. The weight is calculated by assuming the density of 1 g/ml.

Alternative calculations used. Using the image within the 25 per cent count contour to give a reproducible "edge" to the scintigraph, other calculations were carried out similar to those of Larsen (1971).

(1) Length of posterior image.
(2) Area of posterior image.
(3) Area of lateral image.

Validation of method

Less than 24 hours prior to splenectomy a scintigraphic estimate of spleen size was carried out in nine patients. The spleen was removed as part of a cancer operation in four patients and for haematological disorders in five patients. All the spleens removed were macroscopically normal with little

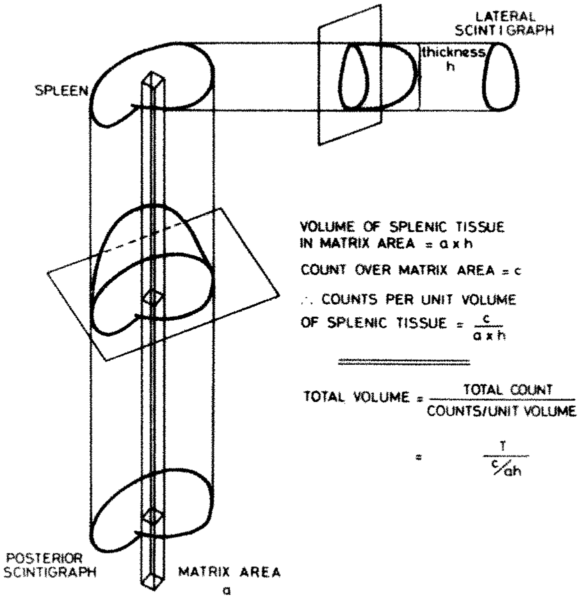
LATERAL SCINTIGRAPH
thickness h
SPLEEN
VOLUME OF SPLENIC TISSUE IN MATRIX AREA = a x h
COUNT OVER MATRIX AREA = c
∴ COUNTS PER UNIT VOLUME OF SPLENIC TISSUE = c / a x h
TOTAL VOLUME = TOTAL COUNT / COUNTS/UNIT VOLUME
= T / c/ah
POSTERIOR SCINTIGRAPH
MATRIX AREA a

FIG. 1.

Interpretation of the splenic image.

disturbance of splenic architecture. Spleens were weighed with a Sartorious balance immediately after excision and again 30 minutes and six hours later. At the moment of excision the spleen is engorged with blood and releasing clamps from the vascular pedicle causes the blood to flow out of the organ. Thus the weight of the spleen on removal is greater than at any time later.

Statistical analysis

A Sumlock 340 "Statistician" was used for the statistical analysis incorporating standard programs for linear regression. The residual mean square and confidence limits were calculated from the variance about the linear regression.

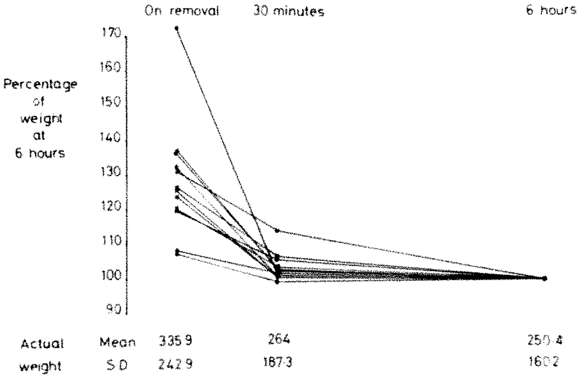

FIG. 2.

Reduction in spleen weight after excision.

TABLE I

Scintigraphic estimate	Spleen wt. stat. (g)	Spleen wt. 30 mins. (g)	Spleen wt. 6 hours (g)
529	635	370	368
527	450	340	340
642	598	446	436
107	95	80	75
287	225	188	182
214	125	100	100
203	105	97	98
326	232	185	170
221	168	140	140

RESULTS

Actual spleen weight

Figure 2 illustrates the phenomenon of weight loss due to blood flow from the spleen after removal; weight is represented as a percentage of the weight six hours after removal. The proportion of initial spleen weight due to blood is variable and the spleen weight recorded after 30 minutes excludes the effect of this variable. The weights recorded at 30 minutes and later allow a more meaningful comparison between the weight of actual splenic tissue and the scintigraphic estimate.

Correlation of spleen weight with scintigraphic "computed volume" estimates

Table I shows actual figures for spleen weight and scintigraphic estimate.

Table II shows the linear regressions of actual weight against scintigraphic estimate using the immediate, 30 minutes and six-hour weights. The results show a better correlation coefficient with the exsanguinated weight of the spleen, 30 minutes and six hours after removal. The accuracy of the estimates are also better at 30 minutes and six hours when the residual mean squares and 95 per cent confidence limits are compared. A graphic representation of the results using the six-hour exsanguinated spleen weight is shown in Fig. 3.

Comparison of the "computed volume" estimate with those used by Larsen *et al.* (1971) based on the 25 per cent count contour to define objectively the edge of the spleen and the six-hour exsanguinated spleen weight are shown in Table III and show the computed volume estimate to be superior.

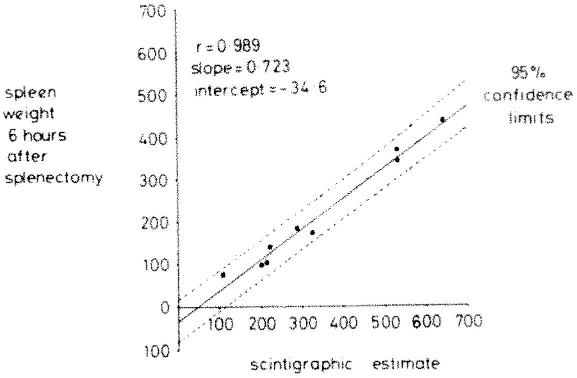

FIG. 3.

Correlation of scintigraphic estimate with spleen weight.

TABLE II

Correlation of actual spleen weight with scintigraphic "computed volume" estimate

Time of weighing spleen	Correlation coefficient (r)	Slope (b)	Intercept	95% confidence limits at $\bar{X}$ (g)	at $\bar{X}$ (g) ±300 g	Residual mean square
On removal	0·959	1·11	−85·7	132·7	151·5	4,129
30 minutes	0·988	0·73	−31·8	44·6	50·9	466·5
6 hours	0·989	0·72	−34·6	45·3	51·4	482

TABLE III

Comparison of new method with those of Larsen (1971)

Method	Correlation coefficient	Residual mean square	95% confidence limits at $\bar{X}$ (g)	at $\bar{X}$ ±300g (g)
Length posterior image	0·824	6,575	167	203
Area posterior image	0·828	6,427	166	223
Area lateral image	0·974	1,046	68	83
Computed volume	0·989	482	45	51

Discussion

The spleen is made up of blood, lymphoid and reticulo-endothelial cells, plasma and connective tissue. A splenic scintigraph is an expression of the removal of labelled red cells from the blood by sinusoidal macrophages. These macrophages represent the functional reticulo-endothelial tissue in the organ. The proportion of spleen weight due to blood is greatest immediately after excision and the flow of blood from the organ thereafter reduces the proportion due to blood and the remaining weight more nearly represents the weight of lymphoid and reticulo-endothelial elements. It is therefore not surprising that the computed volume estimate of spleen size correlates best with the exsanguinated weight of the spleen. Furthermore, it is unlikely that the weight at the moment of excision is the same as the *in vivo* "normal weight".

In this study no patient suffered from portal hypertension and none of the spleens would be engorged *in vivo* and shrinkage would not be expected during splenectomy. During splenectomy for unengorged spleens surgical manipulation can produce kinking of veins and the technique of splenectomy often involves clamping of veins before arteries. These manoeuvres may contribute to engorgement of the spleen and it is not improbable that the immediate weight is greater than the "normal" weight *in vivo*. Both these factors could provide an explanation why correlation with exsanguinated weight should be better, while understanding at the same time that the *in vivo* "normal weight" probably lies somewhere between the "immediate" and "exsanguinated" weight. This may account for the observed differences in the slopes of the regression lines.

Any recorded image of a radioactive source has an ill-defined margin which is further confused by respiratory movements in the living subject. Most accounts estimating spleen size from splenic images do not define which point in the obscure margin is taken to represent the edge of the organ. The "edge" can be drawn by hand (Holzbach *et al.*, 1962; Rollo and Deland, 1970; Larsen *et al.*, 1971) and most estimates of spleen size from radioisotopic images must be based on some interpolation of this sort but the method is not always described (Fischer and Wolf, 1966). Accurate estimates of spleen size should be based on an objective reproducible method of defining the margin of the image. In this study we have used the 25 per cent count contour as the objective definition of the "edge" of the spleen.

Using line-drawing of the splenic margin, Larsen *et al.* (1971) found that various calculations gave the mathematical correlations shown in Table IV. These results give accuracies comparable with our computed volume estimates. In our patients the results obtained employing these same calculations but using the 25 per cent count contour and the spleen weight at six hours are shown in Table III. The correlation coefficients for posterior area and length are inferior to those of Larsen and the accuracy as assessed by the residual mean square and 95 per cent confidence limits suggest that they are at best crude estimates. In contrast, the area of the lateral image

TABLE V

PUBLISHED CORRELATION OF ACTUAL WEIGHT WITH SCINTIGRAPHIC ESTIMATE

Author	Source of spleens	Index used	Correlation coefficient
Larsen *et al* (1971)	Splenectomies (14)	Length posterior image	0·960
	Autopsies (3)	Posterior image area	0·941
		Lateral image area	0·968

which has been advocated for some time as an index of splenic size (Holzbach *et al.*, 1962; Fischer and Wolf, 1966) is confirmed as the most effective simple index.

Nonetheless, in our hands, the computed volume estimate of spleen size provides the best correlation with spleen weight that has hitherto been described and gives the lowest confidence limits. This method provides an accurate means of estimating spleen size in patients with macroscopically normal spleens so that changes in spleen size in association with disease processes can be monitored. We are using this method to assess changes in spleen size in relation to human tumour growth in women with breast cancer. Furthermore, the principles involved in the method can be applied to other organs which can be demonstrated by isotopic scinitigraphy.

ACKNOWLEDGMENTS

We should like to thank Dr. J. L. Whittaker, Mr. D. L. Crosby and Professor L. E. Hughes for allowing us to study patients under their care and Dr. A. S. Bligh for access to the gamma-camera.

This work was carried out while one of us (J.G.R.) was in receipt of a Cancer Research Campaign Fellowship.

REFERENCES

BLENDIS, L. M., WILLIAMS, R., and KREEL, L., 1969. Radiological determination of spleen size. *Gut*, *10*, 433–435.

CLARKE, L. P., LAUGHLIN, J. S., and MAYER, K., 1972. Quantitative organ uptake measurement. *Radiology*, *102*, 375–382.

CONGDON, G. C., and MAKINODAN, T., 1961. Splenic white pulp alteration after antigen injection, relation to time of antibody production. *American Journal of Pathology*, *39*, 697–709.

FISCHER, H. W., 1957. Colloidal stannic oxide animal studies on a new hepatolienographic agent. *Radiology*, *68*, 488–498.

FISCHER, J., and LEON, E., 1969. In *Medical Radioisotopic Scintigraphy*, pp. 381–396 (International Atomic Energy Agency, Vienna).

FISCHER, J., and WOLF, R., 1963. In *Medical Radioisotope Scanning*, Vol. 2, pp. 357–363 (International Atomic Energy Agency, Vienna).

HAMILTON, E. quoted in Tinkler, J., 1971. Measuring the elements in man. *New Scientist*, 728–730.

HOLZBACH, R. T., CLARK, R. E., SHIPLEY, R. A., KENT, W. E., and LINDSAY, G. E., 1962. Evaluation of spleen size by radioactive scanning. *Journal of Laboratory and Clinical Medicine*, *60*, 902–913.

LARSEN, S. M., TUELL, S. H., MOORES, K. D., and NELP, W. B., 1971. Dimensions of the normal adult spleen and prediction of spleen weight. *Journal of Nuclear Medicine*, *12*, 123–126.

LEACH, K. G., KARRAN, S. J., WISBEY, M. L., and BLUMGART, L. H., 1975. In vivo assessment of liver size in the rat. *Journal of Nuclear Medicine*, 16, 380–385.

MCINTYRE, P. A., 1972. Diagnostic significance of the spleen scan. *Seminars in Nuclear Medicine*, *2*, 278–287.

MCINTYRE, P. A., and WAGNER, H. N., 1970. Current procedures for scanning the spleen. *Annals of Internal Medicine*, *73*, 995–1001.

MCRAE, J., and VALK, P. E., 1972. Alteration of ^{99m}Tc red blood cells. *Journal of Nuclear Medicine*, *13*, 399–400.

OLD., L. J., BENACERRAF, B., CLARKE, D. A., CARSWELL, E. A., and STOCKERT, E., 1961. The role of the reticulo-endothelial system in the host reaction to neoplasia. *Cancer Research*, *21*, 1281–1300.

ROLLO, F. D., and DELAND, F. H., 1970. The determination of spleen mass from radionuclide images. *Radiology*, *97*, 583–587.

ROSCH, J., 1965. Roentgenologic possibilities in spleen diagnosis. *American Journal of Roentgenology*, *94*, 453–461.

ROSENBAUM, H. D., LIEBER, L., and PELLEGRINO, E. D., 1964. A routine survey roentgenogram of the abdomen in 500 consecutive patients over 40 years of age. *American Journal of Roentgenology*, *91*, 903–909.

SIGEL, R. M., BECKER, D. V., and HURLEY, J. R., 1970. Evaluation of spleen size during routine liver imaging with ^{99m}Tc and the scintillation camera. *Journal of Nuclear Medicine*, *11*, 689–692.

SIMONSEN, M., 1962. Graft versus host reactions, their natural history and applicability as tools of research. *Progress in Allergy*, *6*, 349–467.

WESTIN, J., LANNER, L. O., LARSSEN, A., and WEINFELD, A., 1972. Spleen size in polycythaemia. *Acta medicina Scandinavica*, *191*, 263–271.

ZELMAN, S., 1958. Necropsy evaluation of gas contrast roentgenologic visualisation of the liver and spleen. *American Journal of Medical Science*, *236*, 747–754.

1976, *British Journal of Radiology*, *49*, 156–160

Gallium-67 imaging to localize urinary-tract infections

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(*Received April, 1975, and in revised form July, 1975*)

ABSTRACT

To differentiate upper from lower-tract urinary infections, 73 patients were imaged with ^{67}Ga citrate. Renal uptake of the radioisotope occurred in pyelonephritis (documented in 47 patients by ureteral catheterization, bladder washout, or histology) with an accuracy of 86 per cent. There were 15 per cent false-positives and 13 per cent false-negatives. ^{67}Ga may prove to be a clinically valuable test in the diagnosis of pyelonephritis. Results are promptly available 24 hours after injection, and it is a non-invasive test that can safely be repeated to follow recurrent infections.

Differentiation of upper from lower urinary-tract infection may present a clinical problem for therapeutic and prognostic reasons (Reeves and Brumfitt, 1968). Ureteral catheterization as described by Stamey, Govan and Palmer (1965) or bladder-washout as reported by Fairley *et al.* (1967) are reliable, but relatively invasive procedures which cannot be routinely applied to all groups studied, *e.g.*, asymptomatic bacteriuria. Thomas, Shelokov and Forland (1974) have recently developed an immunofluorescence test for antibody-coated bacteria in urinary sediment. Using bladder-washout, Jones, Smith and Sanford (1974) have confirmed the promise of this new test in differentiating cystitis from pyelonephritis.

^{67}Ga imaging of the kidneys (Kessler *et al.*, 1974) provides a non-invasive method of localization of infection. In this report we document the validity of this technique by describing the correlation of the gallium scan results with direct, more established and invasive methods of localization in patients suspected of having pyelonephritis.

METHOD

Seventy-three patients with acute or chronic pyuria were studied, their ages ranging from 15 months to 85 years. All had urine cultures (Table I), and most had intravenous urography. When clinically and therapeutically indicated, ureteral catheterization and bladder-washout tests were performed.

^{67}Ga citrate,† 50 μCi/kg, was injected intravenously in all patients 24 hours prior to imaging. Scintillation-camera images of the posterior abdomen were obtained using a Pho-Gamma HP camera fitted with a medium energy diverging collimator. The 184 keV photopeak of ^{67}Ga was selected with a 20 per cent window.

The posterior projection was chosen to allow better visualization of the kidneys. Occasionally, large bowel activity was seen, but the typical configuration of the colon activity did not interfere with identification of the kidneys.

Normal ^{67}Ga uptake by the bony skeleton was used to correctly position the patient for all studies: sacro-iliac joints at the inferior margin of the image, liver and spleen at the upper margin, and the lumbar spine in the mid-line (Fig. 1). Using these landmarks, renal uptake was usually easily defined, but ^{99}Tc^{m}-DTPA was occasionally administered to localize the kidneys in difficult cases (Fig. 2).

RESULTS

Of the 73 patients studied, 47 were ^{67}Ga-positive (one or both kidneys visualized) and 26 were ^{67}Ga-negative. Examples of both a negative and a positive study are shown in Fig. 1. All patients had urine cultures and Table I demonstrates the wider spectrum of organisms recovered in the ^{67}Ga-positive group.

Forty-nine patients had sufficient conventional testing that a diagnosis of pyelonephritis could be confidently made or excluded. Specially, a definite positive diagnosis was made on the basis of a positive bladder-washout, positive ureteral catheterization or histologic changes of acute pyelonephritis. A classic clinical syndrome of fever greater than 102°F, flank pain and pyuria was also considered diagnostic of pyelonephritis. Histologic examination was available for confirmation in six cases. Absence of upper-tract disease was confirmed by either a negative original clean catch urine culture, a negative ureteral culture, or a negative bladder-washout test. These

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†Supplied by New England Nuclear Corporation, North Billerica, Massachusetts.

TABLE I

URINARY ORGANISMS CULTURED IN ALL 73 PATIENTS STUDIED*

Organism	Positive ^{67}Ga scans	Negative ^{67}Ga scans
No organism	8	12
E. coli	15†	9
Klebsiella	6	3
Pseudomonas a.	6	1
Candida sp.		1
Proteus sp.	4	
Streptococcus	3	
Serratia marscens	2	
M. tuberculosis	1	
Enterococcus	1	
Aspergillus fumagatis	1	
Total	47	26

*Greater than 10^5 colonies/ml.

†Another five patients had *E. coli* cultured in addition to other organisms.

TABLE II

^{67}GA SCANS IN 49 PROVEN CASES CORRELATED WITH OTHER PROCEDURES

Examination	Positive ^{67}Ga scans (26 cases) Examination results		Negative ^{67}Ga scans (23 cases) Examination results	
	Pos.*	Negative	Positive	Negative
Fairley test	3	1	1	3
Ureteral culture	5	3	2	2
Renal biopsy/ culture	3	0	0	3
Urine culture (clean catch)	NA	NA	NA	12
Clinical syndrome of acute pyelonephritis	11	NA	0	NA
Total cases	22 (True-positive)	4 (False-positive)	3 (False-negative)	20 (True-negative)

NA: Not applicable; insufficient to specify site of infection.
*"Positive" = Test compatible with upper-tract infection.

criteria were necessary to differentiate a cystitis from a true upper-tract infection.

Table II shows the detailed correlation between ^{67}Ga scan and conventional tests in this sub-set of 49 patients. There were 15 per cent false-positives and 13 per cent false-negatives.

Occasionally, the ureters or bladder were visualized on ^{67}Ga scanning, suggesting ureteral infection or cystitis. In a few patients, focal pyelonephritis was manifest on the scan as a focal lesion. More often, the entire kidney was visualized with a uniform distribution of radioactivity.

Blood and soft-tissue background of ^{67}Ga activity obscured the renal areas at 24 hours in only one-third of the cases studied, and a repeat view at 48 hours was usually superior. In only a few instances the high level of bowel activity necessitated cleansing enemas to improve scan quality.

DISCUSSION

^{67}Ga citrate was originally introduced as a tumour-scanning agent, and now serves an important role in staging neoplasms (Edwards and Hayes, 1970; Littenberg *et al.*, 1973a). Examples of uptake by inflammatory lesions have also been reported (Larson, Milder and Johnson, 1973; Higasi *et al.*, 1972). In a series of septic patients, scans performed at 24, rather than after the usual 72–96 hours, demonstrated ^{67}Ga concentration in suppurative lesions, including infected kidneys (Littenberg *et al.*, 1973b). Unlike the delayed images (at least 72 hours after injection) recommended for tumour surveys, imaging for pyelonephritis can be done at 24 hours, providing prompt and clinically useful information.

The results of the present study suggest that renal imaging with carrier-free ^{67}Ga citrate may be a helpful test in the work-up of patients with suspected pyelonephritis. It is a non-invasive procedure, and overall accuracy is 86 per cent. Radiation dose estimates are acceptably low: 0·41 rad/mCi to the kidneys and 0·26 rad/mCi to the whole body (MIRD Report No. 2, 1973).

Many of the cases reviewed in this study simply confirmed what was obvious by other tests. ^{67}Ga proved most helpful, however, in patients who were allergic to iodinated contrast material, who refused invasive studies, or who had urinary diversion procedures (Fig. 3).

In those patients with positive renal uptake who were re-studied, gallium scans became normal or improved after two or more weeks of antibiotic therapy. Patients who presented with recurrent pyelonephritis showed reversion to positive ^{67}Ga scans. The data suggest that ^{67}Ga scans may well supplement the long-term follow-up of upper-tract infections. A normal scan might abbreviate work-up of persistent bacteriuria.

Many false-positive results can be eliminated by considering all factors which can contribute to a false-positive scan. To distinguish extra-renal from renal uptake, a renal scanning agent can be injected, and the patient imaged in the same position

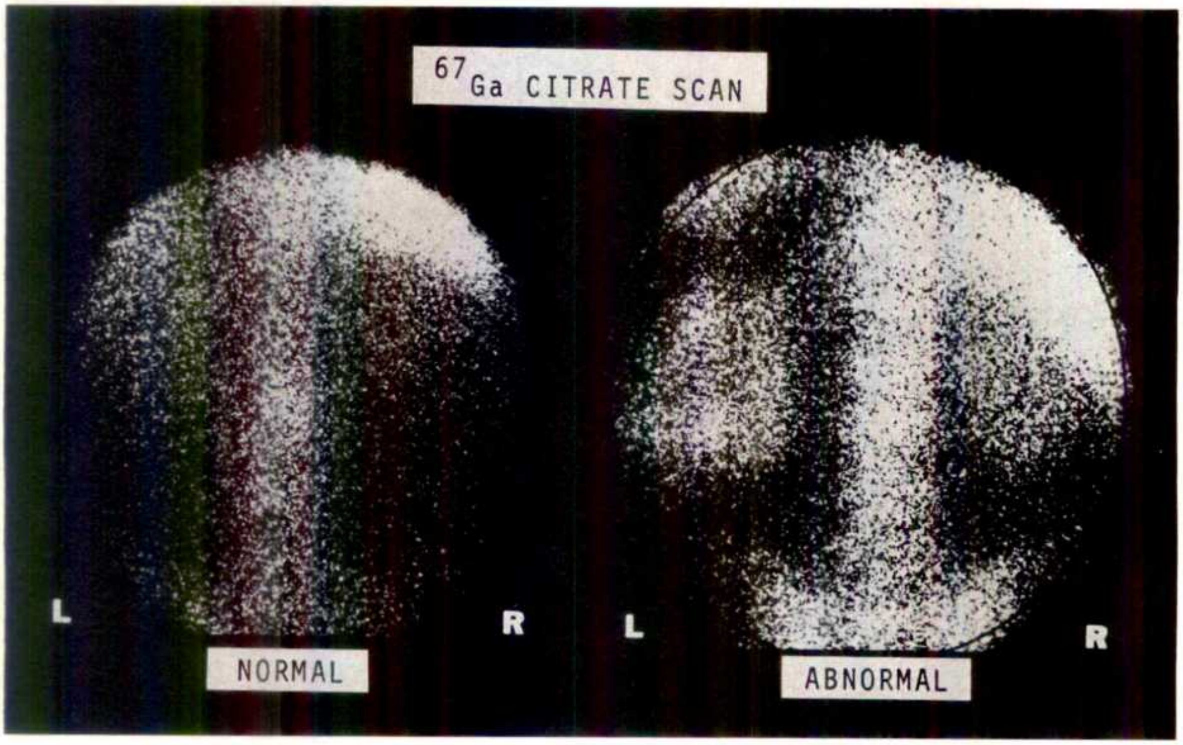

FIG. 1.

On the left, a normal posterior camera image with ^{67}Ga at 24 hours. The patient is a 28-year-old woman with a positive clean catch urine culture, but a normal bladder-washout. On the right, a 30-year-old quadriplegic man with a positive ureteral culture. Both kidneys are intensely labelled with ^{67}Ga; normal liver uptake is seen at the right upper margin.

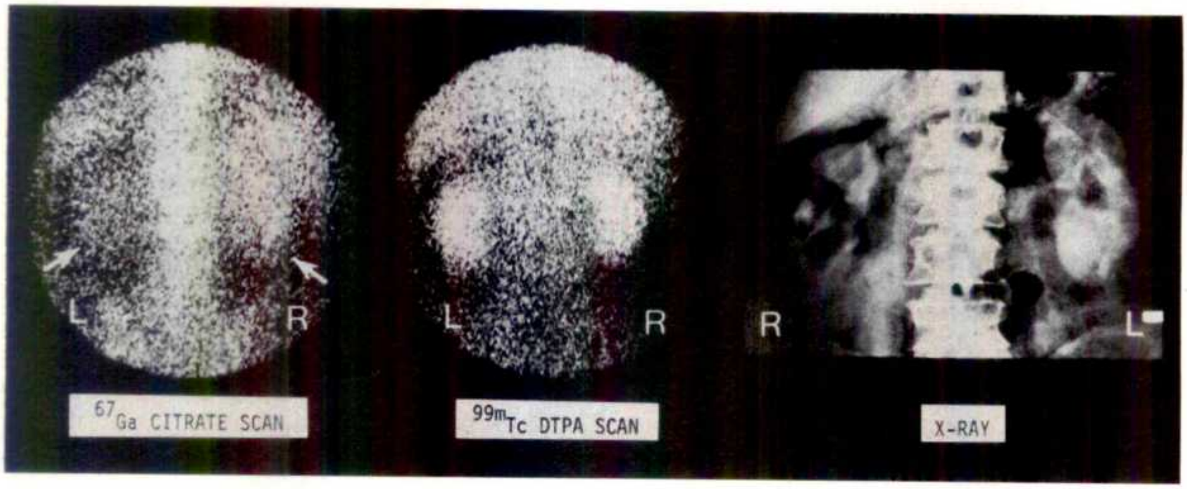

FIG. 2.

This 71-year-old man has carcinoma of the bladder and pyuria The ^{67}Ga images shows mild bilateral renal uptake (arrows). In the centre scintiphoto, a subsequent image with ^{99}Tc^{m}-DTPA verifies the renal location. At the right is the intravenous urogram.

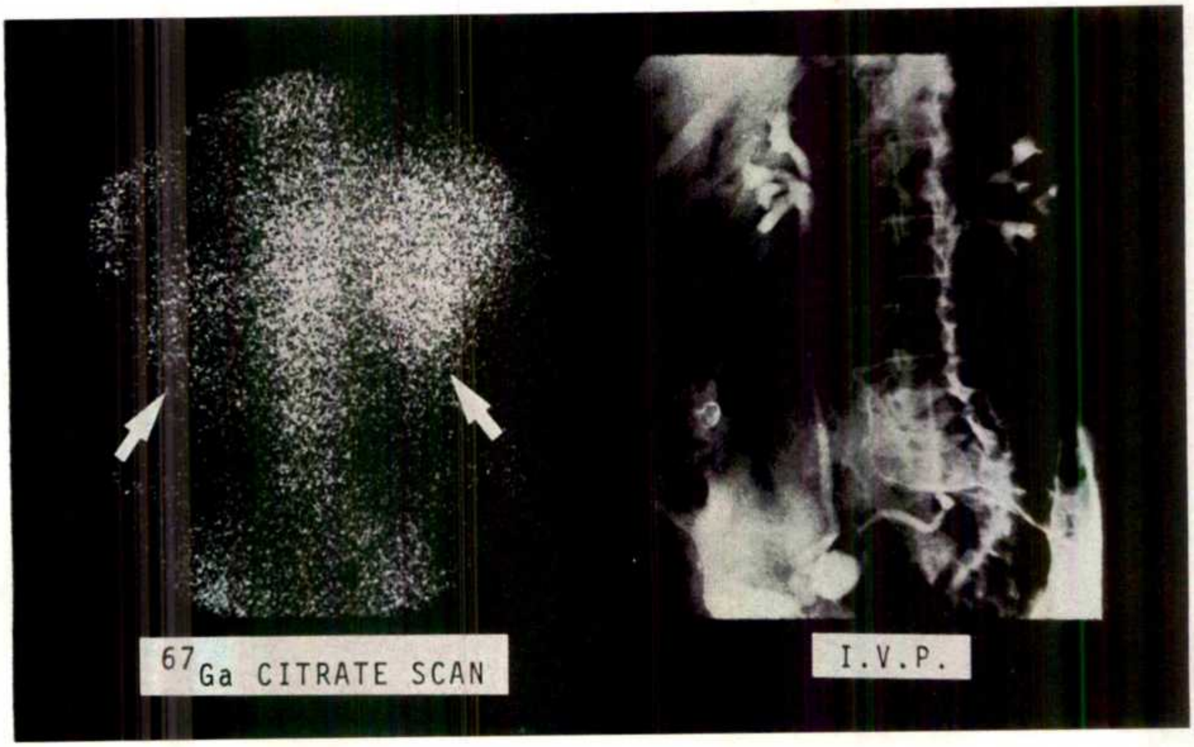

FIG. 3

This 65-year-old man had a previous Bricker procedure as demonstrated on the urogram at right. Loop cultures were positive for *Klebsiella*, and the ^{67}Ga image shows bilateral uptake (arrows).

as for the gallium scan. Repeated enemas can be administered, if necessary, to diminish background bowel activity. At some stages of pyelonephritis, cultures may be negative (so-called "abacterial pyelonephritis" Aoki *et al.*, 1969), and the physician may incorrectly conclude that the ^{67}Ga scan is falsely positive. Other reports have documented ^{67}Ga concentration in recent surgical wounds, renal tumours, retroperitoneal abscesses, and other inflammatory processes (Littenberg *et al.*, 1973b; Blair *et al.*, 1974; Gelrud *et al.*, 1974). These should be kept in mind when clinically relevant in evaluating a scan for the purposes of screening for pyelonephritis.

Additional studies to confirm this work are needed before the ^{67}Ga scan can be accepted as a routine clinical study for the evaluation of urinary-tract infections. ^{67}Ga is approved for general use, however, and cameras or scanners are generally available in hospital practices.

Animal experimentation is currently in progress at our institution to test these patient results. Initial studies in rats and rabbits suggest that 50 μCi/kg of ^{67}Ga is an ideal injection dose. Above this level in small animals even normal kidneys may be faintly visualized. A variable fraction of the injection ^{67}Ga is normally excreted by the kidneys, but no renal visualization is apparent on the scan in the absence of tumour or infection at this recommended dose (Kessler *et al.*, 1974).

There are four methods of localizing urinary-tract infection that now show reliability when compared to each other. Ureteral catheterization and bladder-washout are direct tests. Two centres have so far detected antibody-coated bacteria in the urinary sediment. This may prove a helpful screen, but like bladder-washout, discriminates only upper from lower-tract disease. ^{67}Ga imaging offers a more graphic test that, like ureteral catheterization, is specific for the infected kidney. Of all four tests, only ^{67}Ga is feasible in patients with urinary diversion procedures (*e.g.* ureterosigmoidostomy).

REFERENCES

AOKI, S., INAMURA, S., AOKI, M., and MCCABE, W. R., 1969. "Abacterial" and bacterial pyelonephritis: immunofluorescent localization of bacterial antigen. *New England Journal of Medicine, 281*, 1375–1382.

Blair, D. C., Carroll, M., and Silva, J., 1974. Localization of infectious processes with Gallium citrate Ga 67. *Journal of American Medical Association, 230*, 82–85.

Edwards, C. L., and Hayes, R. L., 1970. Scanning malignant neoplasms with gallium 67. *Journal of the American Medical Association, 212*, 1182–1190.

Fairley, K. F., Bond, A. G., Brown, R. B., and Johnston, G. S., 1967. Simple test to determine the site of urinary tract infection. *Lancet, 2*, 427–428.

Gelrud, L. G., Arseneau, J. C., and Milder, M. S., 1974. The kinetics of 67 Gallium incorporation into inflammatory lesions: experimental and clinical studies. *Journal of Laboratory and Clinical Medicine, 83*, 489–503.

Higasi, T., Nakayama, Y., Murata, A., and Suzuki, S., 1972. Clinical evaluation of ^{67}Ga citrate scanning. *Journal of Nuclear Medicine, 13*, 196–201.

Jones, S. R., Smith, J. W., and Sanford, J. P., 1974. Localization of urinary tract infections by detection of antibody-coated bacteria in urine sediment. *New England Journal of Medicine, 290*, 591–593.

Kessler, W. O., Gittes, R. F., Hurwitz, S. R., and Green, J. P., 1974. Ga-67 renal scans in the diagnosis of pyelonephritis. *Western Journal of Medicine, 121*, 91–93.

Larson, S. M., Milder, M. S., and Johnston, B. S., 1973. Interpretation of the ^{67}Ga photoscan. *Journal of Nuclear Medicine, 14*, 208–214.

Littenberg, R. L., Alazraki, N. P., Taketa, R. M., and Ashburn, W. L., 1973a. A clinical evaluation of gallium-67 citrate scanning. *Surgery, Gynaecology and Obstetrics, 137*, 424–430.

Littenburg, R. L., Taketa, R. M., Alazraki, N. P., and Ashburn, W. L., 1973b. Gallium-67 for localization of septic lesions. *Annals of Internal Medicine, 79*, 403–406.

MIRD Dose Estimate Report No. 2, 1973. *Journal of Nuclear Medicine, 14*, 756.

Reeves, D. S., and Brumfitt, W., 1968. Localization of urinary tract infection. In *Urinary Tract Infection*, pp. 53–67 (Oxford University Press, London).

Stamey, T. A., Govan, D. E., and Palmer, J. M., 1965. The localization and treatment of urinary tract infections: The role of bactericidal urine levels as opposed to serum levels. *Medicine (Baltimore), 44*, 1.

Thomas, V., Shelokov, A., and Forland, M., 1974. Antibody-coated bacteria in the urine and the site of urinary-tract infection. *New England Journal of Medicine, 290*, 588–690.

Book reviews

Elements of Radiation Protection. By R. V. Scheele and J. Wakley, pp. ix+99, illus., 1975 (Springfield, Illinois, Charles C. Thomas), $7.95.

This book is largely derived from lecture courses given by the authors to radiology residents and student X-ray technologists in the United States. The aim has been to explain the principles underlying radiation protection measures using only such physics and mathematics as is essential.

There are 85 pages of text and two appendices: one on units, and one quoting extracts from American Federal regulations on protection. A useful list of references for more detailed information is also given.

The first three-quarters of the book deals with the elementary physical principles underlying the production of radiation and its interaction with matter, and goes on to deal with the biological effects of radiation. The units in which radiation and absorbed energy are measured are explained, and permissible dose limits are described. The principles of radiation protection and radiation monitoring devices are covered briefly but adequately. The last quarter of the book is more relevant to American readers than those in the U.K. Three chapters are used to describe recommendations for the use of X-ray equipment and the reduction of exposure to patient and operator. Most of this information is of course relevant in the U.K., and would be useful to a student radiographer.

The production is remarkably free from misprints, but equation 16 is misleading as printed. It is also misleading on page 87 to give the dimensions in which the röntgen is measured both correctly, and as those of kerma in air. The occasional use of a comma in place of a semi-colon is noted.

The book can be recommended to those requiring a survey of the elements of radiation protection at an introductory level. The quality of the binding should be improved in any future editions.

N. W. Ramsey.

Short-lived Radioactive Gases for Clinical Use. By J. C. Clark and P. D. Buckingham, pp. xii+353, 1975 (London, Butterworth), £9·50.

This excellent monograph sets out in a clear and orderly format the detailed technology for producing gaseous radionuclides suitable for pulmonary function and other clinical work. Inevitably it is a specialist's book, since most doctors and physicists using radioactive gases are more concerned with the clinical aspects of the subject than with details of manufacture, yield, and design of processing systems for radiopharmaceuticals. Furthermore a large proportion of the book is devoted to the really "short-lived" gases, $^{13}N_2$, $^{15}O_2$, ^{11}CO and $^{11}CO_2$, which are of only academic interest to those not in close proximity to a cyclotron. The authors devote little space to ^{133}Xe, presumably because its technology is well known, but do give useful sections on ^{127}Xe and ^{135}Xe, and the radionuclides of krypton, of which ^{81}Kr^{m} has been shown to be of promise for regional ventilation studies. A section on dispensing and clinical facilities brings the subject closer to the hospital department, but if a multiprobe detector system is to be described in such detail, is not a scintillation camera worthy of mention also? For such a specialist book it seems unnecessary to fill even a small chapter with the elements of nuclear physics, but this happens too often in books concerned primarily with the application of radioactive substances to medicine.

With its attention to detail, clear illustrations, and inclusion of useful appendices on mathematical analysis this book is of direct benefit to those working in a cyclotron unit dedicated to clinical investigation. To those of us less fortunate it provides a comprehensive background to the subject, and leads to a better understanding of the problems of supplying hospitals with clinical radioactive gases.

D. M. Ackery.

1976, *British Journal of Radiology*, *49*, 161–165 FEBRUARY 1976

Some *in vivo* effects of π^- mesons in mice

By J. E. Coggle, M.Sc., Ph.D., Myrtle Y. Gordon, B.Sc., Ph.D., Patricia J. Lindop, M.B., Ph.D., D.Sc., M.R.C.P., Jennifer Shewell, B.Sc., Ph.D. and A. J. Mill, B.Sc., Ph.D.

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(*Received February, 1975*)

ABSTRACT

The effect of 70 MeV π^- mesons was studied to determine the effectiveness of such beams against normal tissues *in vivo*. The end points included thymic weight loss, oocyte and bone marrow CFU-S survival and the induction of macroscopic lens opacities. The results indicate that π^- mesons are not significantly more effective for these end-points than more conventional radiation sources such as ^{60}Co γ rays, 220 kVp X rays, and 14 MeV X rays and electrons. Nor was there any detectable difference in RBE between the peak and plateau regions of the π^- meson beam. The significance of these findings is discussed in relation to the published π^- meson RBE values of between 1·4 and 5·0.

Following the suggestion by Professor J. Rotblat, Fowler and Perkins (1961) proposed the possible therapeutic use of negative π^- mesons and preliminary physical experiments were performed by Richman *et al.* (1966). Recent advances have made available beams of biologically significant intensity and momentum spread and a number of *in vitro* biological experiments have been performed which have been reviewed by Raju (1974). A 70 MeV π^- meson beam at the Rutherford High Energy Laboratory, England (Perry and Hynes, 1971), which delivers up to 150 rad h^{-1} has been used in some recent *in vivo* studies in mice. These have included thymus weight loss, oocyte survival, bone marrow CFU-S survival and the induction of macroscopic lens opacities.

MATERIALS AND METHODS

The details of the π^- meson beam and its dosimetry are given in the accompanying paper by Mill, Lewis and Hall (1975). Before all mouse irradiations a depth-dose curve was determined and the position of the peak scanned in both the vertical and horizontal planes to facilitate the positioning of the mice. The 80 per cent isodose curve at the peak covers a volume of $\sim$2 cm^3 which allowed only partial body irradiations in mice. All the mice used were Bts/SAS/4 strain random bred from a closed colony.

Lens opacities

To study the induction of lens opacities, one-day old male and female mice were given irradiation to the head alone: eight mice were irradiated per exposure, four in the peak region simultaneously with four in the plateau of the beam. The mice were restrained in ventilated Perspex containers and so arranged that their heads were within a volume of 2 cm^3. The containers were placed in a $10\times10\times18$ cm^3 Perspex phantom at the depth required for peak or plateau irradiation. Two hundred and fifteen day-old mice were given a range of peak and plateau doses between 40 and 200 rad and compared with 152 sham-irradiated controls. Following irradiation the mice were weighed and examined for macroscopic lens opacities by two independent observers at monthly intervals.

Thymus irradiations

Two and a half week old male and female mice were irradiated using the same procedure as above, with the beam centred on their thymuses. Two mice in the peak were irradiated simultaneously with two in the plateau. The mice were killed 48 hours after irradiation, and their thymus glands dissected out and weighed fresh. Thymic weight loss was calculated as relative thymus weight (mg/100 g bodyweight) expressed as percentage change from the relative weight of sham-irradiated control mice. Young rodents have an incompletely developed pituitary-adrenal stress response (Jailer, 1950), and young mice only begin to exhibit a plasma corticosterone response to stress after 16 days of age (Kakihana, Blum and Kessler, 1974). The thymic involution measured here is therefore essentially a radiation-induced rather than a systemic stress effect, despite the relatively long duration of the irradiation procedures. Sham irradiated mouse thymus weights were within 2–3 per cent of those of non-irradiated litter mates left with the mother.

Ovary irradiations

Two and a half week old mice were irradiated as for the thymus, but with the beam centred on the ovaries, which 48 hours later were removed, fixed and serially sectioned at 5 μm and scored for small oocyte-stages.

Bone marrow irradiations

Femoral marrow from 12 SAS/4 donors was pooled and suspended in Eagle's minimum essential medium at a concentration of 5×10^8 nucleated cells in $2 \times 2 \times 0{\cdot}5$ cm^3 Perspex irradiation chambers. Such cell suspensions were placed at various positions in the depth-dose curve and irradiated at 1 rad minute^{-1}. Similar irradiations were done for comparison using ^{60}Co γ rays at 1 rad minute^{-1}. During the extended irradiation times the cells were agitated at 30-minute intervals to resuspend and oxygenate them. The efficiency of this oxygenation was checked using the O_2 cathode method (Davies, 1973). Previous experiments had shown that the unavoidable insults involved in centrifugation and resuspension of the concentrated cells, the frequent agitation and a temperature of 25°C throughout lasting up to four hours did not affect the viability of the colony forming cells. However, these procedures and the low dose-rate did severely limit the total dose it was possible to give. Recipient mice were given 1,100 rad ^{60}Co γ rays at 18 rad minute^{-1} and 24 hours later they were injected intravenously with known numbers of irradiated cells. Thirty-two recipients were used per dose group and ten days after irradiation and transplantation they were killed and their spleens placed in Bouin's solution to facilitate the scoring of spleen colonies (Till and McCulloch, 1961). Such colonies are produced by spleen colony forming cells (CFU-S) which are believed to be haemopoietic stem cells.

Reference curves

To assess the effectiveness of π^- mesons for these endpoints a number of comparative irradiations were performed using ^{60}Co γ rays, 14 MeV electrons and X rays, 14 MeV neutrons and 220 kVp X rays, and regression lines fitted to the data are used as reference curves.

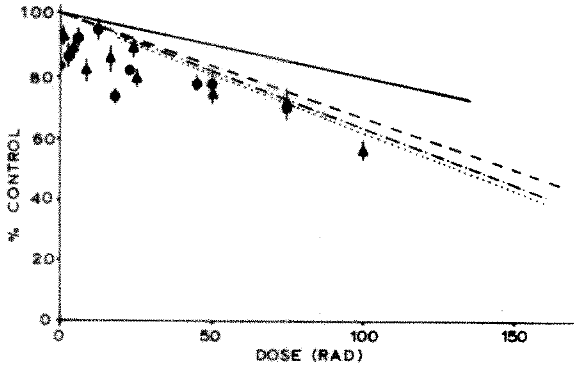

FIG. 1.

Thymic weight in two-and-a-half week old Bts/SAS/4 mice as a percentage of sham-irradiated controls and as a function of dose for peak and plateau π^- mesons and other radiation sources. Average of eight mice per point.

▲ peak π^- mesons.
● plateau π^- mesons.
········ 14 MeV X rays 400 rad/minute^{-1}.
– – – – 14 MeV electrons 400 rad/second^{-1}.
———— 220 kVp X rays 12·5 rad/hour^{-1}.
–·–·–·– 220 kVp X rays 800 rad/hour^{-1}.

RESULTS

Figure 1 shows thymic weight loss as a percentage of controls in two and a half week old mice following π^- mesons and a variety of other radiations. The

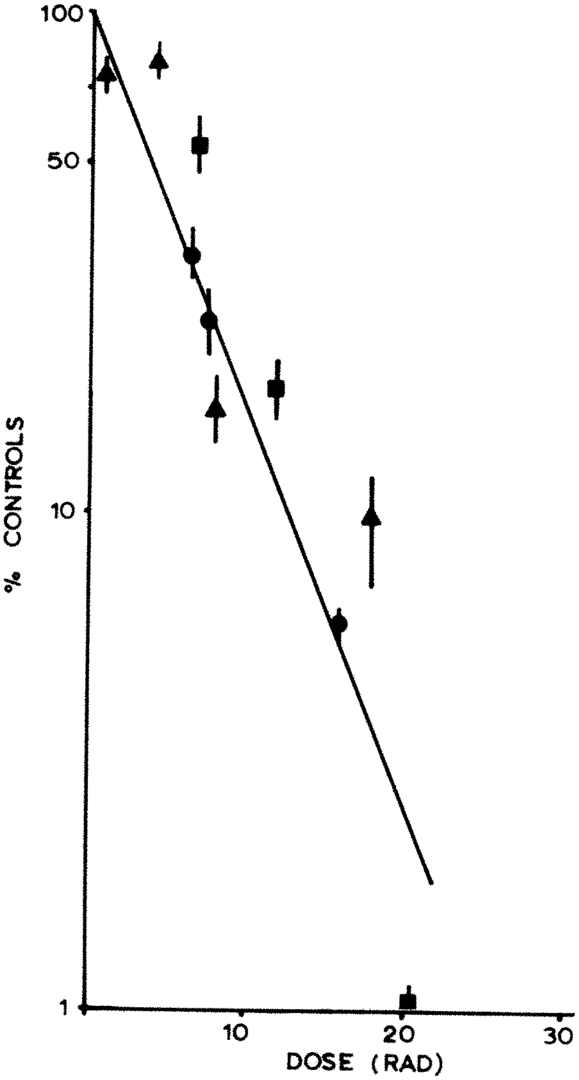

FIG. 2.

Small oocyte survival in two-and-a-half week old Bts/SAS/4 mice.

▲ peak π^- mesons.
● plateau π^- mesons.
■ 14 MeV neutrons.
———— fitted line to 14 MeV electron and X ray data.

dose-rate for the peak and plateau points at less than 50 rad was 10–12·5 rad hour^{-1} while that for 50–100 rad points was 100 rad hour^{-1}. The data show that there is no biological difference between irradiation in the plateau and peak regions of the π^- meson beam, and no difference between the response to π^- mesons and to the reference radiations although π^- mesons seem to be slightly more effective (RBE *circa* 1·3) than low dose-rate X rays.

Figure 2 shows the response of small oocytes in two and a half week old mice for a variety of radiations and once again there seems to be no difference between response in the peak and plateau regions of the π^- meson beam and an RBE of 1 for π^- mesons compared to the reference radiations.

In Fig. 3, the dashed lines show the 95 per cent confidence limits of a full survival curve for CFU-S for two-year-old Bts/SAS/4 donors irradiated at 400 rad second^{-1} with 14 MeV electrons which has a $D_0=119\pm3{\cdot}6$ rad and $n=0{\cdot}9\pm0{\cdot}1$ (Proukakis, Coggle and Lindop, 1969). Using mice of the same age the π^- meson CFU-S points are not significantly displaced from these limits. Also in Fig. 3 the dotted lines show the 95 per cent confidence limits of a survival curve for 30-week-old Bts/SAS/4 mice for 14 MeV electrons, $D_0=126\pm6$ rad and $n=1{\cdot}4\pm0{\cdot}3$ (Proukakis *et al.*, 1969). The three π^- meson points are the CFU-S survival of marrow samples placed in the plateau, peak and behind the peak—4·8 cm, 14·6 cm and 16·1 cm in the Perspex phantom respectively. The three samples were irradiated simultaneously and the data show no detectable differences in the relative biological effectiveness of peak/plateau π^- mesons.

Figure 4 shows the rate of appearance of macroscopic lens opacities in SAS/4 mice given irradiation at a day old to the head alone. The first discernible opacities appeared in a few mice as early as two months after radiation, but the majority did not appear until four to five months post-irradiation. No distinction is made in Fig. 4 between mice with unilateral opacities and those having bilateral opacities since the appearance of an opacity in one eye was quickly followed in 80–90 per cent of mice by a similar opacity in the opposite eye. Figure 4 also shows that the incidence of opacities remained very stable between 6 and 12 months post-irradiation. The majority of the opacities scored were minute and chalky white and even 12 months post irradiation more than 80 per cent of them remained small,

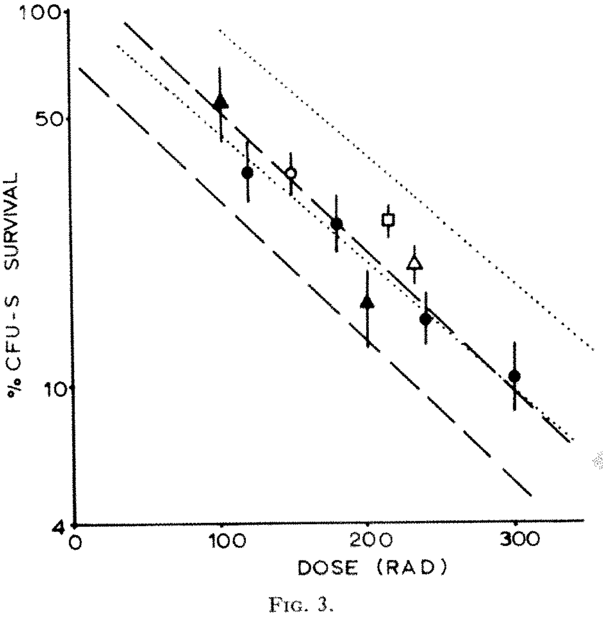

FIG. 3.

The —— —— lines show the 95 per cent confidence limits of a full CFU-S survival curve for two-year-old Bts/SAS/4 mice. ▲π^- meson points; ●low-dose rate ^{60}Co γ ray points. Similarly the .... lines show 95 per cent confidence limits of a CFU-S survival curve for 30-week old Bts/SAS/4 mice. △ peak π^- mesons, ○ pleateau π^- mesons and ☐ behind the peak π^- mesons—three marrow samples irradiated simultaneously.

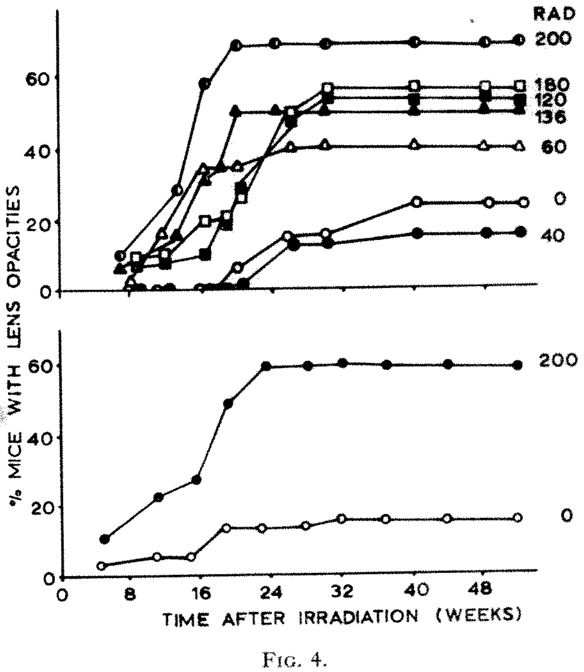

FIG. 4.

Rate of appearance of macroscopic lens opacities in day-old mice given head-only irradiation with π^- mesons (upper graph) and ^{60}Co γ rays (lower graph) at 1 rad minute^{-1}.

only 19 per cent having enlarged to become gross opacities occupying more than 50 per cent of the lens.

Figure 5 shows the per cent of mice with opacities 12 months post-irradiation as a function of dose and shows that the relationship is approximately linear. In previous work using day old mice given 14 MeV X rays at 400 rad minute^{-1} only gross opacities were scored involving >50 per cent of the lens and in Fig. 6 these data are plotted together with data for gross opacities induced by π^- mesons and 200 rads ^{60}Co γ rays.

Discussion

In the past few years significant advances have been made in the study of the biological effect of π^- mesons. The endpoints studied have included cell survival *in vitro* in a number of mammalian cell lines, the induction of polyploidy and chromosome aberrations, the inhibition of growth in ascites tumours and *Vicia faba* root tips, spermatogonial and lymphocyte survival and arginine reversal in yeast (Raju and Richman, 1972). The RBE values for peak π^- mesons for these endpoints range from 1·4–5·0.

However, the conclusion to be drawn from the results given in this study of four *in vivo* endpoints in mice is that π^- mesons are not significantly more effective than conventional radiation sources. Nor is there any detectable difference in biological effect between peak and plateau radiation. This conclusion, which is at variance with much of the literature, must be qualified. First, it needs to be stressed that the severe limitations of field size, total dose and available beam time forced us to study extremely sensitive endpoints—which in the case of oocyte, thymocyte and CFU-S survival are probably single event phenomena and therefore insensitive to dose-rate and LET effects. Second, much of the data in the literature derives from experiments done with nearly monoenergetic π^- meson (momentum spread $\sim$5 per cent) beams at Berkeley and CERN which have large LET differences between peak and plateau, whereas the Rutherford π^- beam has a momentum of spread of $\sim$13 per cent. It has not proved possible to detect a peak to plateau difference for *in vivo* endpoints, although such differences are detectable in cell culture systems in our laboratory (Mill *et al.*, 1975) and others (Nias *et al.*, 1974) and for *Vicia faba* root growth (Winston, Berry and Perry, 1973), and for chromosome aberrations in human lymphocyte cultures (Lloyd, Purrot and Dolphin, 1974; Lloyd *et al.*, 1974). The *in vivo* results given here indicate that RBE values for therapeutically useful beams of π^- mesons may not be large and that the significant peak:plateau ratios obtained with nearly monoenergetic π^- mesons are unobtainable *in vivo* with beams of larger momentum spread. Nevertheless, much more needs to be known about the physical composition of π^- mesons and their biological effects *in vivo*, before a final judgement can be made upon their possible therapeutic use.

Acknowledgments

The authors wish to acknowledge the help given by the staff of the Rutherford Laboratory, especially Dr. D. H. Reading and Mr. M. A. Hynes. The work was also supported by a grant from the Cancer Research Campaign.

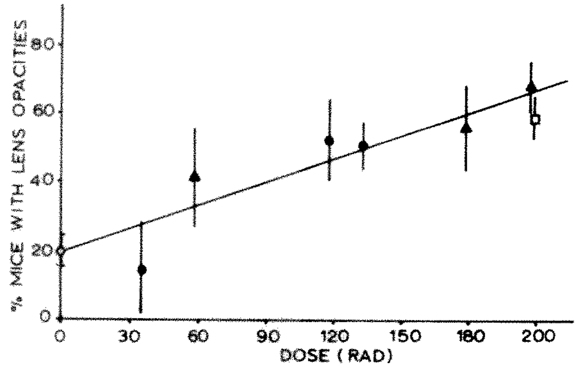

Fig. 5.

Percentage of mice with lens opacities 12 months after irradiation to the head only at a day old.

▲ peak π^- mesons.

● plateau π^- mesons.

☐ ^{60}Co γ rays.

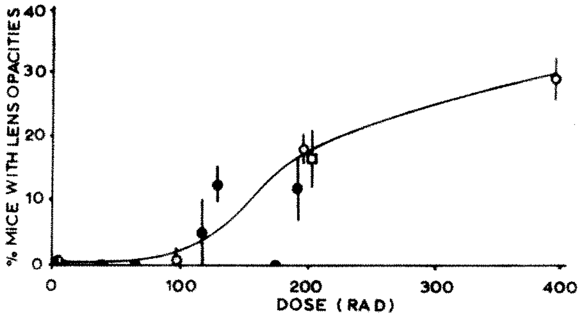

Fig. 6.

Percentage of mice with gross lens opacities 12 months after radiation with 14 MeV electrons at 400 rad second^{-1} (○), π^- mesons (●), and ^{60}Co γ rays (☐) at 1 rad minute^{-1}.

REFERENCES

DAVIES, R. W., 1973. Oxygen concentration and radiation response: studies in mammalian normal and tumour tissues. Ph.D. Thesis, University of London.

FOWLER, P. H., and PERKINS, D. H., 1961. The possibility of therapeutic applications of beams of negative pi-mesons. *Nature (London)*, *189*, 524–528.

JAILER, J. W., 1950. The maturation of the pituitary adrenal axis in the newborn rat. *Endocrinology*, *46*, 420–425.

KAKIHANA, R., BLUM, S., and KERSLER, S., 1974. Developmental study of pituitary adrenocortical response in mice: plasma and brain corticosterone determination after histamine stress. *Journal of Endocrinology*, *60*, 353–358.

LLOYD, D. C., PURROTT, R. J., and DOLPHIN, G. W., 1974. Chromosome aberrations produced in human lymphocytes by a 70 MeV negative pi-meson beam. *Radiation Research*, *59*, 206 (abstract).

LLOYD, D. C., PURROTT, R. J., DOLPHIN, G. W., and READING, D. H., 1974. An investigation of the characteristics of a negative pion beam by means of induced chromosome aberrations in human peripheral blood lymphocytes. Rutherford Laboratory publication –74–150 (pre-print).

MILL, A. J., LEWIS, J. D., and HALL, W. S., 1976. Response of HeLa cells to irradiation with π^- mesons. *British Journal of Radiology*, 49, 166–171.

NIAS, A. H. W., GREENE, D., MAJOR, D., PERRY, D. R., and READING, D. H., 1974. Determination of RBE values for fast neutrons and negative π^- mesons using frozen HeLa cells. *British Journal of Radiology*, *47*, 800–804.

PERRY, D. R., and HYNES, M. A., 1971. A pion beam for radiobiological and dosimetric studies: using a proton synchroton external target. *CERN Publication 71–16*, *1*, 220–230.

PROUKAKIS, C., COGGLE, J. E., and LINDOP, Patricia J., 1969. Effect of age at exposure on the bone marrow stem cell population in relation to 30-day mortality in mice. In *Radiation Biology of the Fetal and Juvenile Mammal*, edited by Sikov, M. R., Mahlum D. D. (USAEC).

RAJU, M. R., 1974. Negative pions in radiotherapy: a brief review. *European Journal of Cancer*, *10*, 211–215.

RAJU, M. R., and RICHMAN, C., 1972. Negative pion radiotherapy: Physical and radiobiological aspects. *Current Topics in Radiation Research Quarterly*, *8*, 159–233.

RICHMAN, C., ACETO, H., RAJU, M. R., and SCHWARTZ, B., 1966. The radiotherapeutic possibilities of negative pions: preliminary physical experiments. *American Journal of Roentgenology*, *96*, 777–790.

TILL, J. E., and MCCULLOCH, E. A. Direct measurement of radiation sensitivity of normal bone marrow cells. *Radiation Research*, *14*, 213–222.

WINSTON, B. M., BERRY, R. J., and PERRY, D. R., 1973. Response of *Vicia faba* to irradiation with a beam of negative π^- mesons. *British Journal of Radiology*, *46*, 541–547.

Book reviews

Radiation Science at the National Physical Laboratory, 1912–1955. By E. E. Smith, pp. 114 (16 illus.), 1975 (London, Her Majesty's Stationery Office), £5·00.

It all began officially in 1912 when the new British National Radium Standard, prepared in Vienna and checked and polished by Madame Curie herself, was deposited at the National Physical Laboratory in Teddington. Or perhaps we should look to an earlier date, the beginning of 1906, when the Röntgen Society held a meeting to consider the need for a radioactive standard to act as a basis for X-ray dosimetry. From these beginnings to the present day, the National Physical Laboratory has been closely associated with the progress and development of radiology in this country, and with the Institute itself.

Eric Smith, who spent many years on the staff of the Laboratory, has delved deeply into the archives to compile a detailed history of the contributions of the National Physical Laboratory to developments in radiation science. The main fields covered are, of course, radiation measurement and standardization, and radiation protection but there is much on the early development of radiography and X-ray crystallography. There is also a bonus of wartime stories and pictures of the antics of E. E. Smith, W. Binks and others, radiographing enemy parachute mines in conditions which look extremely dangerous.

To someone like the present reviewer, who has spent the greater part of a lifetime in the field, this review inevitably evokes a high level of nostalgia. The excitement of radiation measurement with a gold-leaf electroscope or similar device has been overwhelmed in the sophistication of modern measuring apparatus.

Names of physicists prominent in British Institute of Radiology affairs crop up frequently in this history. G. W. C. Kaye is almost a legendary figure in both National Physical Laboratory and British Institute of Radiology and we are reminded that such distinguished hospital physicists as T. A. Chalmers, D. E. A. Jones, J. R. Clarkson, H. F. Cook and Joan McAllister served their apprenticeship at Teddington. If the history could have been brought up to date, we would have seen the reverse process of hospital physicists such as Jennings, Kemp and Burns returning to staff the present-day Division of Radiation Science.

With all respect to a fellow physicist, the literary style of this book is rather pedestrian, but this is perhaps inevitable when so much history must be crammed into so few pages. Nevertheless, it is a history which needed to be written, and in these days of highly sophisticated radiation technology, Mr. Smith has performed a valuable service in recording how it all began.

J. E. ROBERTS.

Wertigkeit Radiologischer Methoden Niere-Leber-Pankreas. Edited by A. Breit, pp. 122, 1975 (Stuttgart, Georg Thieme) DM 39·80.

A paperback entirely in German, the composite effort of 17, mostly university departments of radiology, in Germany and Austria, stimulated by a joint congress held in Vienna in 1973. The intention has been to compare the level of diagnostic information obtainable from more recent X-ray, isotope and ultrasonic methods with other more established forms of investigation in order to determine, for a number of clinical situations, the diagnostically most fruitful methods and their optimum sequence of application.

By far the greater part of the text deals with the diagnosis of renal disease. This is an entirely retrospective group of studies based on a large patient material but fragmented by many variables of examination technique. Ultrasonography does not yet occupy a sufficiently important place. Findings are critically evaluated and brought together in two useful chapters written by a renal physician and by a urologist.

The part concerning the liver and pancreas comprises an article on angiography in liver disease; the same authors also discuss the angiography of pancreatic disorders, very briefly and without comparative evaluation.

About 200 references are contained in the bibliography. There are numerous tables, no illustrations.

H. HERLINGER.

1976, *British Journal of Radiology*, *49*, 166–171

Response of HeLa cells to irradiation with π^- mesons

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(*Received February, 1975*)

ABSTRACT

HeLa cell suspensions were irradiated at various depths of Perspex in a beam of 70 MeV π^- mesons. The dose-rate in the Bragg peak varied between 40 rad hour^{-1} and 150 rad hour^{-1}. The cells were assayed *in vitro* for loss of reproductive integrity.

The results for irradiation in the peak indicated an RBE of about 2·1 when compared to the response obtained using ^{60}Co γ-rays at comparable dose-rates. At dose-rates of 100–150 rad hour^{-1}, the RBE peak-to-plateau was about 1·4, whilst at lower dose-rates, the RBE peak-to-plateau was about 1.

Since 1961, when Fowler and Perkins first published calculations showing the advantages of π^- mesons for radiotherapy, there has been much interest in using these particles for radiobiological experiments. The depth-dose curve for a π^- meson beam is characterized by a plateau region followed by a rise to a peak region, after which it falls off sharply to a very low value. As the dose in the peak region is due partly to nuclear fragments produced by the capture of stopped π^- mesons, it is expected that the relative biological effectiveness (RBE) in this region would be high compared to the plateau region and to conventional radiations.

Due to the small number of π^- meson sources available, and also their very low dose-rates, there have so far been few biological investigations using mammalian cells. A π^- meson beam for radiobiological research is available in England at the Rutherford High Energy Laboratory (Perry and Hynes, 1971). This is a fairly low intensity beam designed to concentrate particles over an area of approximately 2×2 cm^2. The dose-rate available in the peak at the commencement of these experiments was about 40–60 rad hour^{-1}, but has since risen to 160 rad hour^{-1}. In order to investigate the biological effectiveness of this beam, we have used HeLa cell suspensions which, following exposure to radiation, have been scored, *in vitro*, for loss of reproductive integrity.

THE BEAM

The π^- meson beam is produced by bombarding a target with 7 GeV protons extracted from a proton synchrotron. The number of π^- mesons produced depends on the size and composition of the target, as well as on the number of protons extracted. For the early experiments we used a 10 cm. long copper target. With the maximum proton beam this produced a dose-rate of 60 rad hour^{-1} in the peak. More recently we have used a 10 cm long tungsten target, and this, together with an upgrading in the synchrotron, has increased the dose-rate to a maximum of 160 rad hour^{-1}. Π^- mesons produced at an angle of 94 deg. to the extracted beam are collected and focused using a beam line consisting of five quadrupoles and one bending magnet (Perry and Hynes, 1971). Particles of momenta up to 220 MeV/c can be transported. The momentum spread was 13 per cent at full width, half maximum. For these experiments 70 MeV π^- mesons were used producing a peak ionization at a depth of 14–15 cm in Perspex (density$=$1·19 g cm^{-3}) with a peak-to-plateau ionization ratio of approximately 1·4:1. The main contaminants in the beam are μ^- mesons and high-energy electrons. M^- mesons are produced by π^- meson decay in flight with a mean life-time of $1{\cdot}6 \times 10^{-8}$ seconds, and their numbers are minimized by using a short beam line. Electrons are mainly produced by π° meson decays to γ rays which will occur in the target, and the subsequent pair production and electron cascades. The number of electrons is less than 20 per cent of the total number of particles and is minimized by the use of a narrow target. In the peak region the contribution to the dose by the electrons and μ^- mesons was less than 5 per cent each. Neutron contamination contributed less than 1 per cent to the dose. A more detailed description of the physical characteristics of this beam can be found in Reading (1975).

DOSIMETRY

The cells were irradiated in a Perspex phantom of cross-sectional area 20×20 cm^2. The phantom consisted of a number of Perspex sheets, 0·6 cm thick, any of which could be replaced by similar sheets designed to hold ionization chambers for dosimetry, or to hold cell suspensions. Prior to irradiation of the cells, the beam was scanned both horizontally and vertically using a 0·6 cm^3 ionization chamber. This made it possible to find the central position of the beam and enabled accurate positioning of the phantom. The dose-rate was within 10 per cent over an area approximately 1·7×1·8 cm^2. A depth-dose curve was determined by moving a thimble chamber through the phantom and taking ratios of its reading to that of a transmission chamber situated at the beam exit port.

Corresponding depth-dose curves for copper and tungsten targets are shown in Fig. 1. The peak-to-plateau ratio using the copper target (Fig. 1A) was 1·51:1 with the peak dose-rate at a depth of 14·7 cm in Perspex. Using the tungsten target (Fig. 1B) the peak-to-plateau ratio was 1·36:1 with the peak at a depth of 14 cm. These values refer to measurements taken in a solid Perspex phantom. The possible perturbing effect of introducing cell suspensions into the phantom was measured by checking ionization readings at several depths with the suspensions in position. The results of these measurements are also shown in Fig. 1. They indicate no significant alteration in the structure of the peak.

The cell suspensions were irradiated at various depths in the phantom in containers measuring 2·0×1·9 cm^2 in cross-section, and 0·5 cm deep. The cells were thus contained within the 80 per cent isodose area. The exposures were monitored by a 0·6 cm^3 ion chamber placed at a depth of 1·91 cm in the phantom. A ^{60}Co-γ calibration was used to estimate the doses, which were corrected for the depth at which the cells were irradiated.

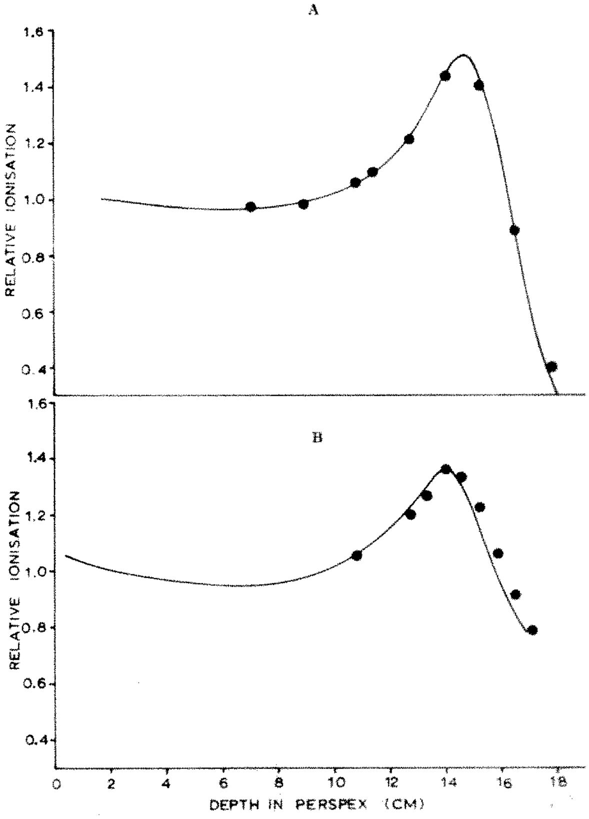

FIG. 1.

Central axis depth-dose curve for 70 MeV π^- mesons. (A) Copper target. (B) Tungsten target.
—— solid phantom.
● cell suspensions in phantom.

CELL CULTURE AND EXPERIMENTAL PROCEDURE

The cell line used for these experiments was derived from a sub clone of the HeLa S-3/Oxf line and was grown in Eagles Minimum Essential Medium plus 28 per cent calf serum. Prior to experimentation the cells were grown in monolayer culture and taken to the Rutherford Laboratory. About one to two hours before irradiation the cells were trypsinized and suspended in Eagles Minimum Essential Medium for Suspension Cultures at a concentration of ~2×10^6 cells cm^3. About 2 cm^3 of suspension was put into each of the cell containers which were placed at predetermined depths in the phantom, and the beam switched on. At regular intervals the beam was switched off, the ion chamber reading noted and a small sample (~0·1 cm^3) of cell suspension removed from each container. The volume was made up with fresh medium to minimize air gaps, and the exposure restarted. A sample was also removed from a control suspension situated outside the beam. The cells samples were diluted into a larger volume, counted, diluted and plated. The plates were incubated at 37°C for 14 days when they were fixed and stained. The clones were counted under a dissecting microscope at ×4 magnification using the usual criterion of 50 or more non-giant cells per clone.

Figure 2 shows the effect of time in the irradiation chambers on the viability and multiplicity of the HeLa cell suspension when kept at room temperature. There is no significant increase in multiplicity, but by 24 hours the viability had dropped to ~40 per cent of its initial value. This is not unduly large, and most exposures, especially those at the high dose-rates, were of much shorter duration.

RESULTS

The results are presented as survival curves determined at several depths in the Perspex phantom. Figure 3 shows the results for the low dose-rate

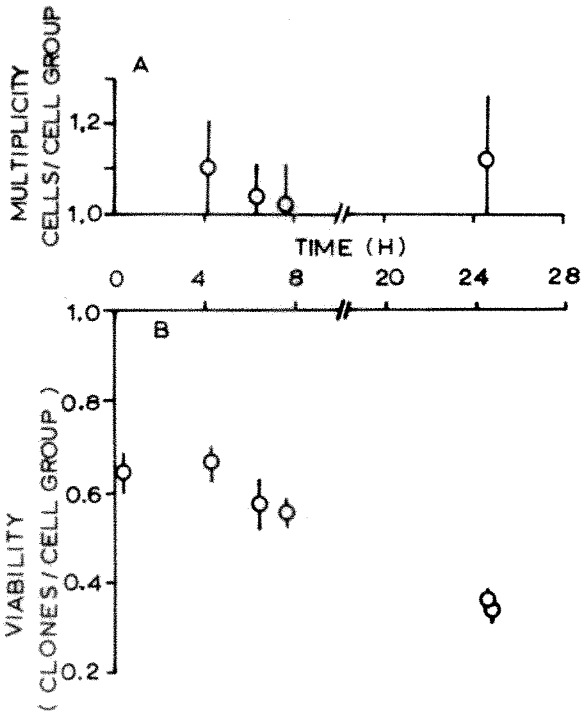

FIG. 2.
The effect of length of time at room temperature on (A) the multiplicity; (B) the viability of HeLa cell suspensions.

experiments using a copper target in the proton beam. The dose-rate in the peak was 40 or 60 rad hour^{-1}. The data are for three depths—one in the plateau region (Fig. 3A) and two in the peak region (Fig. 3B and C). The actual depths and ionization levels (normalized to an ionization of 1 at a depth of 1·91 cm) are indicated. The lines are fitted by eye.

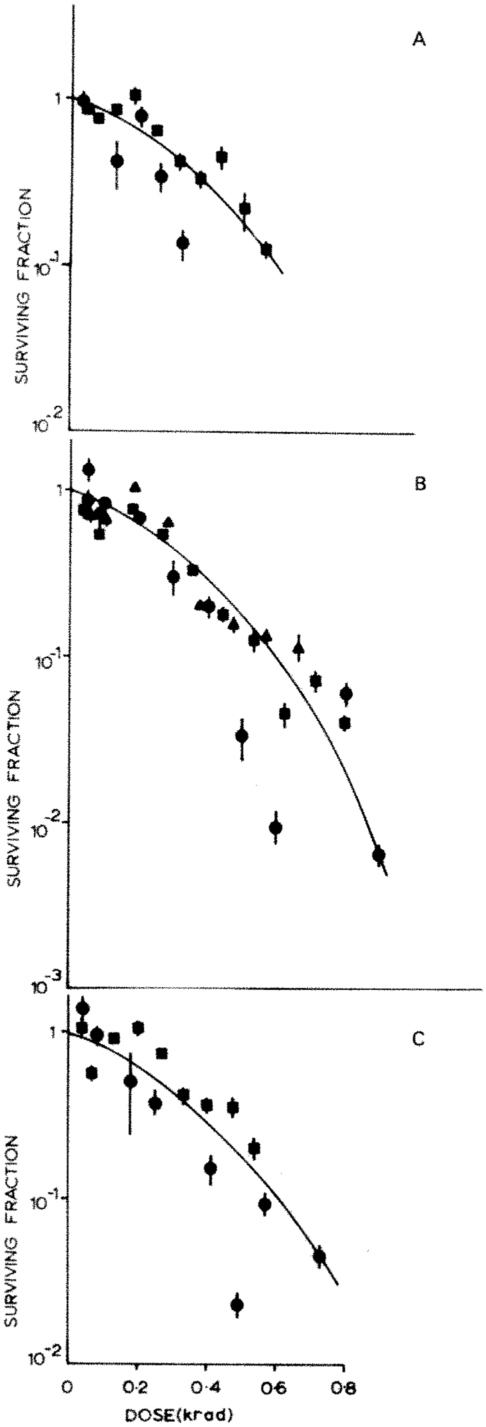

FIG. 3.
HeLa cell survival curves for π^- meson irradiation using the copper target.

(A) Plateau
● 40 rad hour^{-1} } depth = 4·8 cm;
■ 25 rad hour^{-1} } relative ionization = 0·97

(B) Peak
● 60 rad hour^{-1} } depth = 13·7 cm;
■ 40 rad hour^{-1} } relative ionization = 1·39
▲ 40 rad hour^{-1} depth = 14·9 cm; relative ionization = 1·49

(C) Back of peak
● 50 rad hour^{-1} depth = 15·0 cm; relative ionization = 1·15
■ 30 rad hour^{-1} depth = 16·2 cm; relative ionization = 1·06

The data show no obvious difference in the survival curves at any of the depths used. However, more recent data, obtained using the tungsten target and at dose-rates 100–150 rad hour^{-1} do show differences in the response of HeLa cells at various depths. These results are shown in Fig. 4. Irradiation at 13·7 cm (in the centre of the peak—see Fig. 1B) is most effective. Irradiation at 12·4 cm depth is slightly less effective, while irradiation in the plateau (4·8 cm) and just behind the peak (14·9 cm) are least effective. At the 20 per cent survival level, the RBE peak-to-plateau is ~1·4. The response at 13·7 cm

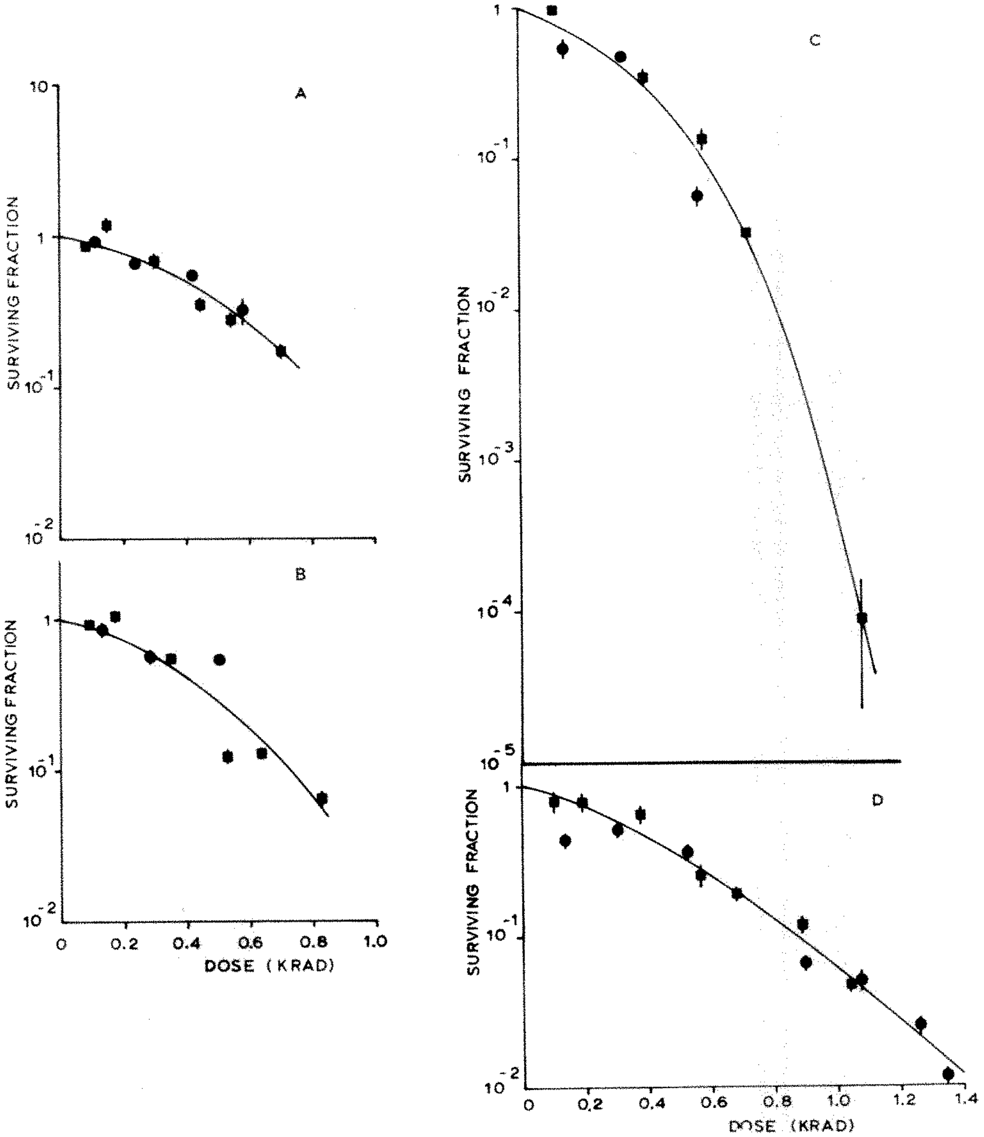

FIG. 4.

HeLa survival curves for π^- meson irradiation using the tungsten target.

(A) Plateau	■ 85 rad hour^{-1} ● 110 rad hour^{-1}	depth = 4·8 cm; relative ionization = 0·96
(B) In front of peak	■ 95 rad hour^{-1} ● 135 rad hour^{-1}	depth = 12·4 cm; relative ionization = 1·19
(C) Peak	■ 110 rad hour^{-1} ● 150 rad hour^{-1}	depth = 13·7 cm; relative ionization = 1·35
(D) Back of peak	■ 100 rad hour^{-1} ● 140 rad hour^{-1}	depth = 14·9 cm; relative ionization = 1·22

depth is similar to the response in the three positions used for irradiations using the copper target.

For comparison purposes, two experiments were done using conventional radiation at suitable dose-rates. The results are shown in Fig. 5 where ^{60}Co γ rays at 55 rad hour^{-1} and 195 rad hour^{-1} have been used. The experiments were done using the same techniques as were used for the π^- meson exposures. There is no difference in the response at these two dose-rates. Π^- mesons (peak) have an RBE of 2·1 compared to γ rays at the 20 per cent survival level. The RBE π^- mesons (plateau) to γ rays at the 20 per cent level is 1·5.

Discussion

The data presented here clearly show the increased effectiveness of π^- mesons compared to conventional radiation at comparable dose-rates. There is evidently no dose-rate effect observed for either π^- mesons in the peak or for γ rays in the range 40–150 rad hour^{-1}. However, the data obtained in the plateau (and to a lesser extent in the post-peak position) show differences between "low" dose-rate exposures (*i.e.* those done using the copper target) and the higher dose-rate exposures (tungsten target). The lower dose-rate appears to be the more effective. Thus, the RBE peak-to-plateau for low dose-rates is ~1, while at higher rates it is ~1·4. This difference is not explicable as a dose-rate effect (the higher dose-rate should be the more effective); nor can it be explained by supposing that the tungsten target increases the low-LET component in the beam (no physical evidence from depth-dose measurements (Reading, 1975)). In the post-peak position, estimation of the dose to the cells is less accurate due to the sharply falling dose-level with distance in this region, and this may account for some differences between experiments.

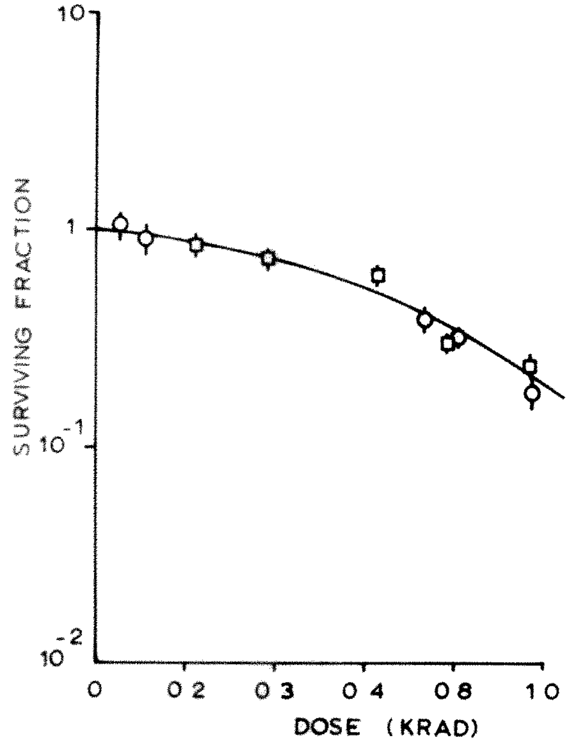

Fig. 5.

HeLa survival curve for ^{60}Co γ ray irradiation at low dose-rates.

○ 55 rad hour^{-1}.

☐ 195 rad hour^{-1}.

Other mammalian data obtained using this same π^- meson beam show RBE values in the peak ranging between 1 and ~2, and peak-to-plateau effect ratios of between 1 and 1·86. Lloyd *et al.*, 1974 find no dose-rate effect in the peak and report a peak-to-plateau ratio of ~1·5 for chromosome aberrations in human lymphocytes. The RBE compared to conventional radiation is ~2. Nias *et al.* (1974) used frozen HeLa cells. The RBE in the peak was 1·86—in good agreement with the results reported in this paper. A determination in the plateau using one point indicated an RBE peak-to-plateau also of 1·86.

Coggle *et al.* (1975) have used several mammalian *in vivo* systems. In none of their end-points do they report a difference in effectiveness peak to plateau. The RBE relative to conventional radiation was 1 for the induction of lens opacities in mice, for bone marrow CFU-S survival and for oocyte depletion. For thymus weight loss the RBE was ~1·3. Thus, these systems show no change in effectiveness with depth and very little change compared to conventional low dose-rate radiation.

The data available from other π^- meson sources was reviewed by Raju and Richman (1972). RBE values for π^- mesons in the peak would seem to lie in the range 1·5–5·0, depending on the end-point and the biological system used. It seems that RBE values depend more on the biological factors involved, than on the physical characteristics of a particular π^- meson beam (*i.e.* momentum spread, dose-rate, etc.). It is still important, however, to find out more about the physical make-up of π^- meson beams before any decision is made as to whether π^- mesons are suitable for radiotherapy. Much more work needs to be done using both *in vitro* and *in vivo* mammalian systems on the effectiveness of π^- mesons at varying depths. Further experiments using the HeLa cell system are planned to investigate the depth-survival profile of the beam for both aerobic and hypoxic cells. This sort of experiment is more likely to tell us whether π^- mesons will be radiotherapeutically useful than a single determination of an RBE value in the peak and plateau regions.

ACKNOWLEDGMENTS

The authors wish to acknowledge the help given by the staff of the Rutherford Laboratory, especially Dr. D. H. Reading and Mr. M. A. Hynes. The work was also supported by a grant from the Cancer Research Campaign.

REFERENCES

COGGLE, J. E., GORDON, Myrtle Y., LINDOP, Patricia J., SHEWELL, Jennifer, and MILL, A. J., 1976. Some *in vivo* effects of π^- mesons in mice. *British Journal of Radiology*, *49*, 161–165.

LLOYD, D. C., PURROTT, R. J., DOLPHIN, G. W., and READING D. H., 1974. An investigation of the characteristics of a negative pion beam by means of induced chromosome aberrations in human peripheral blood lymphocytes. Rutherford Laboratory-74-150 (Pre-print).

NIAS, A. H. W., GREENE, D., MAJOR, D., PERRY, D. R., and READING, D. H., 1974. Determination of RBE values for fast neutrons and negative π mesons using frozen HeLa cells. *British Journal of Radiology*, *47*, 800–804.

PERRY, D. R., and HYNES, M. A., 1971. A pion beam for radiobiological and dosimetric studies: using a proton synchrotron external target. *CERN Publication 71-16*, *1*, 220–230.

RAJU, M. R., and RICHMAN, C., 1972. Negative pion therapy: physical and radiobiological aspects. *Current Topics in Radiation Research Quarterly*, *8*, 159–233.

READING, D. H., 1976. Physical characteristics of the negative pi-meson radiological beam at the Rutherford Laboratory. (In course of publication.)

Book review

Writing Scientific Papers in English. An ELSE-Ciba Foundation Guide for Authors. By Maeve O'Connor and F. Peter Woodford, pp. 116, 4 tables, 9 illus., 1975 (Amsterdam, Associated Scientific Publishers and New York, American Elsevier), $7.95.

This comprehensive and clearly written book originated in discussions of the European Association of Editors of Biological Periodicals (ELSE) over the period 1967–73. The authors describe all the stages in the preparation of an article for publication, and the text contains much thoughtful and detailed advice. In the Foreword, Knut Faegri, Chairman of the ELSE Style Manual Committee comments that "English has taken the place once held by Latin in the world of learning": the authors rightly give much attention to English prose style (p. 41 "Some scientists have a mania for using abstract names") but in addition cover all those problems of organization and presentation that authors must overcome in transferring to a few blank sheets of paper an intelligible account of a complex series of studies recorded in files and note-books over periods of months or years.

The book has nine chapters, five appendices, a bibliography and an index. The first five chapters cover planning the paper, preparation and drafting, and the last four submission, responding to the editor and proof correction. In Chapter 3 there is excellent advice under the heading "Write the First Draft Quickly". "Settle down at a time and place which will allow you to remain undisturbed for several hours. Collect all the material you have prepared . . . If the paper is short try to finish the draft at one sitting . . ."

In Chapter 4 "Revising" there is a fine section on style—problems with verbs, pronouns and nouns, (p. 40: "Excessive use of the passive voice. It is absurd and mentally lazy to use the passive voice in every sentence . . . The right place for a verb in the passive is in a sentence like 'the cows were milked twice a day' when there is no need to identify the milkmaid.") problems of verbosity, pomposity, imprecision and punctuation (*e.g.* p. 43: "If you always choose elaborate words instead of simple ones, you will soon be trapped into using words *wrongly*.")

Chapter 9 "Correcting the Proofs" concludes with the comment "You may wonder why it takes so long for your paper to get into print?": a detailed line diagram provides an answer to the question and shows 17 separate stages in the journey from author to journal subscriber. Appendix I lists 29 steps in the preparation of a paper.

The authors are evidently disciples of Ernest Gowers, Eric Partridge and Arthur Quiller-Couch and their book should find a place on many bookshelves beside those classical works *Plain Words*, *Usage and Abusage* and *The Art of Writing*.

This erstwhile editor of THE BRITISH JOURNAL OF RADIOLOGY can recommend the book to novices and experienced authors, of any mother tongue; he hopes that his successor will find his task a little eased if the book receives the attention it well deserves.

One request to the publishers: the attractive hard back cover makes the book very suitable for libraries, but a wider sale among individual authors would probably be secured for a cheaper cloth covered edition.

N. G. TROTT.

1976, *British Journal of Radiology*, *49*, 172–175

Technical note

On-line beam data acquisition for a dedicated radiotherapy planning computer

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(*Received May, 1975*)

Digital computers are now widely used for calculating absorbed dose distributions in radiotherapy and a number of commercial systems such as the RAD 8 (Digital Equipment Co., and SHM Nuclear Inc.), PC12 (Artronix Inc.) and Philips TPS (Philips Medical Systems) have been developed for this purpose. The greatest single problem encountered when implementing such systems is that of preparing beam data in a computer compatible form. In many cases, isodose curves are the only data available at the time a computer system is installed and the conversion of these to tabular form is both laborious and error prone. An alternative method of data preparation is therefore desirable and the two most viable solutions are:

(1) calculation of beam-data tables using a computer program based upon a mathematical or physical model,

(2) direct measurement of dose distributions in tabular form.

Calculation methods, for example Cunningham (1972) can yield very good results, particularly when applied to ^{60}Co dose distributions; however, the modification of this type of program to suit a particular treatment machine is not always straightforward. A trial and error procedure may be required in which program parameters are repeatedly modified; this can be very time-consuming, and the end product may not be entirely satisfactory. Clearly, such problems, which arise from the lack of suitable input data, are avoided if the beam data is measured directly in a form which is suitable for direct input into the computer.

When a treatment machine is installed, it is normal practice to make comprehensive dose measurements, and the additional labour involved in preparing data for use by a computer treatment planning system is minimized if the basic measurements are made in a tabular form. In the case of installations where measurements already exist in the form of isodose curves, remeasurement for computer use is apparently unattractive because of the labour involved. However, if an automated beam measurement technique is used, the complete remeasurement of a treatment machine can be so rapid that it will take less time than any other method of beam data preparation.

An apparatus, which produces paper tape or similar media, may be specially constructed to automate the measurement of beams, but this will be complex and costly (Blackmore and Naylor, 1975). When a dedicated computer is available, a much simpler and relatively inexpensive system can be made by making an on-line connection with the water phantom (Glenn *et al.*, 1969), and it is evident that the same computer for which beam data will be required may be advantageously used for the initial measurement of the data. This paper describes an automated method of beam measurement which utilizes the standard RAD 8 treatment planning system (Bentley and Milan, 1971). This technique has been successfully used to prepare data for a Mullard SL75 linear accelerator and a T.E.M. Mobaltron F100 Cobalt Unit.

EQUIPMENT AND MEASUREMENT

Absorbed dose measurements are made using a conventional water phantom and ionization chamber, but the position of the chamber is controlled by stepping motors connected to the PDP-8 computer. The output from the ion chamber is connected to one of the analog channels of the computer.

The ionization chamber is a PTW Simplex Micro Chamber with a volume of 50 mm^3 and an internal diameter of 3 mm which produces an output of 10 pA rad^{-1} second^{-1}. A varactor diode amplifier (Analog Devices Type 310) is used to measure the voltage developed by the ionization current across a $10^9 \Omega$ resistor. This amplifier has an input impedance in excess of $10^{11} \Omega$ and produces an output in the range 0–10V which is directly compatible with the existing analog channels of the computer. An additional buffer amplifier with unity gain is used to drive the current into a 100 m cable between the plotting tank and the computer which is situated in a totally separate part of the hospital. The ionization chamber is driven in two orthogonal directions within the water phantom (30 × 30 × 40 cm) using a rectilinear scanning mechanism (Fig. 1). The drive is provided by two stepping motors (SLO SYN type HS50L) which move the chamber in 0·2 mm increments at a speed of up to 300 increments/second. For measurement purposes, this was reduced to 50 increments/second (*i.e.* 10 mm/second). The signal input requirements of the stepping motor drive circuits are electrically equivalent to those of the standard PDP-8 interface normally used to drive a 'Calcomp' type digital X–Y plotter. The necessary program code can therefore be generated with very little effort.

Ionization chamber measurements are made at intervals of 0·2 mm across the radiation beam at five selected depths in the water phantom. To minimize the effect of noise, some 60 samples are recorded at each measurement point. This is the largest number of analog to digital conversions possible in the time available with the chamber in motion at the stated speed. The absorbed dose rate as calculated from the mean of these 60 samples has an estimated error of 0·3 per cent of the maximum absorbed dose rate, *i.e.*, the build-up dose on the central axis. For measurements on a linear accelerator, an additional ionization chamber with its own varactor diode amplifier is used to provide a reference. This second chamber is mounted in a fixed position close to the beam axis to monitor fluctuations in machine output. The signals from both amplifiers are fed through a multiplexer into the computer, and their ratio is calculated digitally. This avoids the need for an analogue ratio circuit. Because the linear accelerator produces very short pulses—1·6 μseconds duration at 2·5 mseconds intervals in the case of the MEL SL75 machine—the time constant of each amplifier must be long enough to overcome effects due to fluctuations in output, but short enough to avoid errors caused by the dose reading lagging behind the positional information. Because there was no obvious method of determining the time constant of the system, a procedure was devised to ensure that it was not too long. This was done simply by driving the ionization chamber at twice the normal scanning speed across the penumbra of the linear accelerator beam. This is the largest dose gradient which will be encountered in practice, and the resulting plot was found to be unchanged at this increased speed.

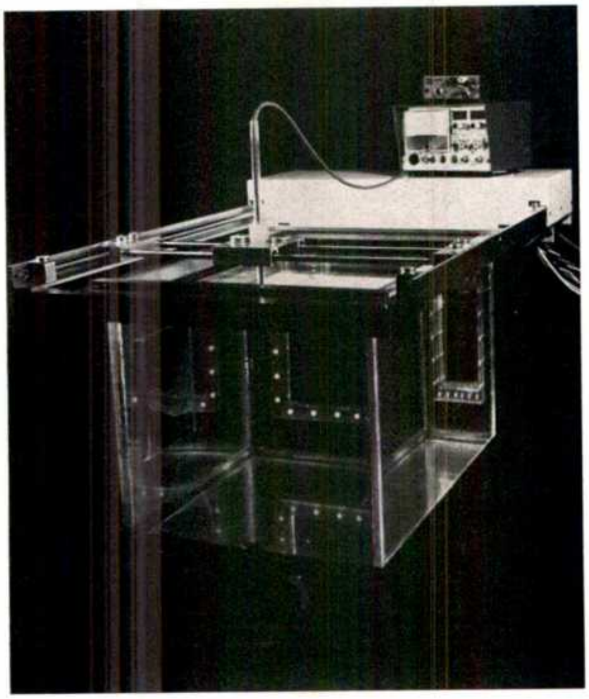

FIG. 1.

Plotting tank with ionization chamber mounted on gantry for two-dimensional drive by stepping motors. (The varactor diode amplifiers for the ionization chambers are shown standing on the stepping motor housing for ease of photography.)

COMPUTER CONTROL

An interactive program is used to measure the profiles and central axis values for each beam. As each profile is recorded, it is displayed on the storage oscilloscope of the computer system, and a facility is provided to restart the measurement of a beam if any of its five profiles are considered unacceptable. This feature has been used occasionally when spurious electrical noise was apparent on the profile display. Facilities are also provided for the position of the profile centre and the 80 per cent or 50 per cent widths to be calculated. This information is used to check the starting position of the ionization chamber and the alignment of the plotting tank. The field size calibration of the collimator of the treatment machine may also be checked.

It was considered desirable to smooth the data from the SL 75 linear accelerator to remove fluctuations of up to 0·5 per cent of the maximum dose. The dose gradient at points in a beam profile is dependent upon position, and so an algorithm was developed which allowed for this. This technique uses averages over 33 points in regions where the

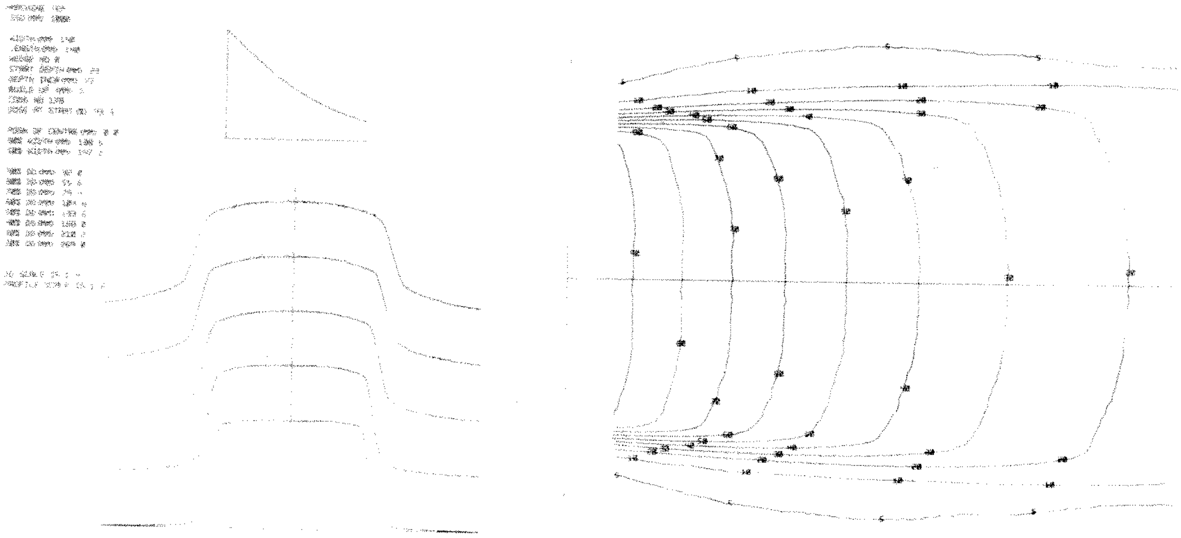

Fig. 2.

Typical output from the special program used for examining the measured data.
Top left: central axis depth dose data.
Bottom left: profiles at five depths.
Right: isodose curve generated from the same data.
Far left: data entered by user followed by numeric results.

profile is linear, but progressively reduces this number as the profile becomes more curved. The algorithm is incorporated into two distinct programs, one of which produces isodose curves directly and, as explained below, as accurately as possible; the other is used to prepare the tables for the RAD 8 programs. Curves obtained from the first program make possible the estimation of any errors in the final output produced by the treatment planning system. The former programs produce isodose curves via an intermediate matrix which has a grid spacing of 3 mm. This program also produces plots of the central axis and profile data and lists the positions of the isodose lines on the central axis. The latter information may be plotted as a function of equivalent square to provide a consistency check. Typical output from this program is shown in Fig. 2. The second program selects the required doses from the profiles and central axis data and stores these in the form required by the RAD 8 programs; facilities are provided in this program to examine the numerical value of points in a newly prepared beam data table.

Discussion

The data table required to specify a beam for the RAD 8 treatment planning system consists of the doses at 17 points on the central axis and the dose ratios at only 47 points on each of the five profiles (Milan and Bentley, 1974). The most direct method of obtaining this data would be to measure doses only at the specific points required by the beam data tables. However, in the above system data is recorded at intervals of 0·2 mm which are so small that the data may be treated as a continuous function. This has the following advantages:

1. Continuous curves can be produced for a quick visual verification that the data appear reasonable.
2. Smoothing procedures may be carried out to reduce noise without significant degradation of the data.
3. Small errors in ionization chamber position which may arise due to backlash or incorrect centering may be readily corrected. By comparison, error correction on tabulated data requires complex interpolation procedures.
4. The exact positioning of points in the beam table can be chosen after the measurements have been completed. This is useful because information gained from profile measurements may influence this decision.
5. The data may be converted to isodose curves using a method which is more accurate than that used by the treatment planning system. The latter is a compromise between accuracy, speed of calculation and memory size with the result that

small errors are detectable in the penumbral region of a beam. These errors are considered insignificant for treatment planning purposes (Bentley and Milan, 1971) but it is desirable that information concerning them should be available. Such information is readily obtainable from isodose curves which are produced directly from beam data which has been recorded as a virtually continuous function. The only disadvantage of recording data in this manner is that the requirement for bulk data storage on magnetic tape is increased. However, the resulting inconvenience and expense are minimal.

The time required with this system to measure a single beam is approximately five minutes, and all the data for one treatment machine may be collected in a few days. This compares very favourably with a commissioning time of many weeks by traditional methods. The long distance which often physically separates the computer and the machine under measurement causes only minor inconvenience.

The measurement of data in tabular form has the advantage that both suitable tables and isodose curves may be generated. This is because isodose curves may be obtained very easily by interpolation of tables but the converse is not true; if isodose curves are measured as the prime data, tables can be produced by interpolation only with great difficulty. We are satisfied that the procedure reported in this note is the only approach which provides a complete solution to the problem of beam data preparation for RAD 8 and similar free standing computer systems.

ACKNOWLEDGMENTS

We wish to thank Mr. D. Hill for construction of the mechanical components of the plotting tank, and Mr. S. P. Newbery and Mr. R. W. Kent for design and construction of the varactor diode amplifier circuit and the control electronics for the plotting tank.

REFERENCES

BENTLEY, R. E., and MILAN, J., 1971. An interactive digital computer system for radiotherapy treatment planning. *British Journal of Radiology*, *44*, 826–833.

BLACKMORE, V. J., and NAYLOR, G. F., 1975. Digital measurement system for radiation dose distribution. *Physics in Medicine and Biology*, *20*, 314–317.

CUNNINGHAM, J. R., 1972. Scatter-air ratios. *Physics in Medicine and Biology*, *17*, 42–51.

GLENN, W. V., BODICKY, A. L., FELDMAN, A., and GLENN, R., 1969. "A signal plotter operated remotely under the control of a small computer". Presented at the Fifty-fifth Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November 30–December 5.

MILAN, J., and BENTLEY, R. E., 1974. The storage and manipulation of radiation dose data in a small digital computer. *British Journal of Radiology*, *47*, 115–121.

Book review

Roentgen Examinations in Acute Abdominal Diseases. By J. Frimann-Dahl, pp. xiv+617, 1974 (Illinois, U.S.A., Charles C. Thomas), $29.50.

The re-editing of a classic text is always something of an event, and the appearance of the third edition of Frimann-Dahl's *Acute Abdomen* is another milestone in radiological literature.

The format of the book is similar to the second edition, but the newer procedures of arteriography in evaluating acute abdominal conditions are dealt with in considerable detail. This is perhaps not surprising in view of the pioneering role that the author's department at Ulleval Hospital played in establishing this technique.

A welcome, but a sad commentary on modern life is the detailed account of the examination of abdominal trauma—a feature of increasing prominence in the radiologist's daily work.

It is difficult to find any real faults in such a magnificent work but perhaps a more detailed description of the medical conditions which mimic an acute abdomen, such as "dia betic abdomen", "porphyria", etc. would be helpful.

The increasing age of the general population throws a special responsibility on the radiologist as the "acute abdomen" in the elderly seldom has the dramatic clinical signs that present in the younger age group. An acute cholecystitis with perforation of the gall-bladder may occur with surprisingly few clinical signs, and it is important that clinicians should give due accord to the radiological findings. Such signs are described in considerable detail. Also, metastatic peritoneal malignancy which may present as a subacute abdomen is a problem which frequently presents difficulties in diagnosis in the elderly.

It is perhaps unfortunate that a large proportion of acute abdominal examinations occur outside normal working hours and the interpretation of the films are often done under conditions which are not conducive to achieving the best results. The author in his preface rightly draws attention to the need to develop this expertise which can only be obtained by constant contact with the problem which implies a ready availability of radiological opinion at all times.

This text is probably far too detailed for the surgeon to be greatly attracted to it, but all radiologists, whether in training or in practice, should study and appreciate the experience of a lifetime that has gone into compounding this book.

It surely must merit a prominent place in every radiologist's library and a place within easy reach of the X-ray reporting station.

ERIC SAMUEL.

1976, *British Journal of Radiology*, *49*, 176–177

Case reports

Septal lines in a case of asthma with eosinophilia

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(*Received April, 1974, and in revised form July, 1975*)

The radiographic manifestations of pulmonary eosinophilia have been well documented, but to our knowledge the finding of septal lines in a case of asthma with eosinophilia has not been recorded.

Case history

R.K., a 23-year-old male, presented with severe breathlessness of recent onset. Two days before admission he developed a sore throat and cough, and felt breathless and progressively more ill. He had a history of asthma since childhood, and was currently taking Franol and Salbutamol. He has had at least two courses of steroids in the past. His mother is asthmatic.

On examination he was breathless, but not cyanosed, and had a pyrexia (102°F). There were scattered rales and rhonchi throughout both lungs. His expiratory peak flow-rate was 200. A chest radiograph at this time revealed patchy shadowing throughout the lungs with the presence of septal lines. The heart size and pulmonary vasculature were within normal limits.

The following investigations were performed to exclude bacterial and fungal infections.

Sputum culture was negative for fungi and mycobacterium and grew only normal mouth commensals. *Serum precipitins* to *Aspergillus fumigatus* and skin testing to *Aspergillus* were negative, though the skin test to house mites was positive.

Initially he had a WBC of 14,000 with 2 per cent eosinophils rising to 7 per cent of 7,500 WBC two days after admission.

On admission he was initially treated with aminophylline. The next day the patient showed some clinical improvement, and was started on antibiotics and a course of steroids (prednisone 5 mg t.d.s.). This gave rise to rapid improvement both clinically and radiologically. The eosinophil count returned to 2 per cent a month later after treatment with steroids. The steroid therapy was tailed off and the patient remained well.

A diagnosis of pulmonary eosinophilia was made in view of the high blood eosinophil count and the response to steroids. The first chest radiograph showed ill-defined opacities throughout both lung fields (Fig. 1A and B) in a mainly peripheral distribution, with well-marked septal lines at the bases and radiating from the hila. These changes cleared rapidly after treatment with steroids, and became normal four days later (Figs. 2A and B).

Discussion and radiology

The conditions in which septal lines may become visible on the chest radiograph have been reviewed by Trapnell (1973). They have been described by Ngan *et al.* (1971) following the administration of

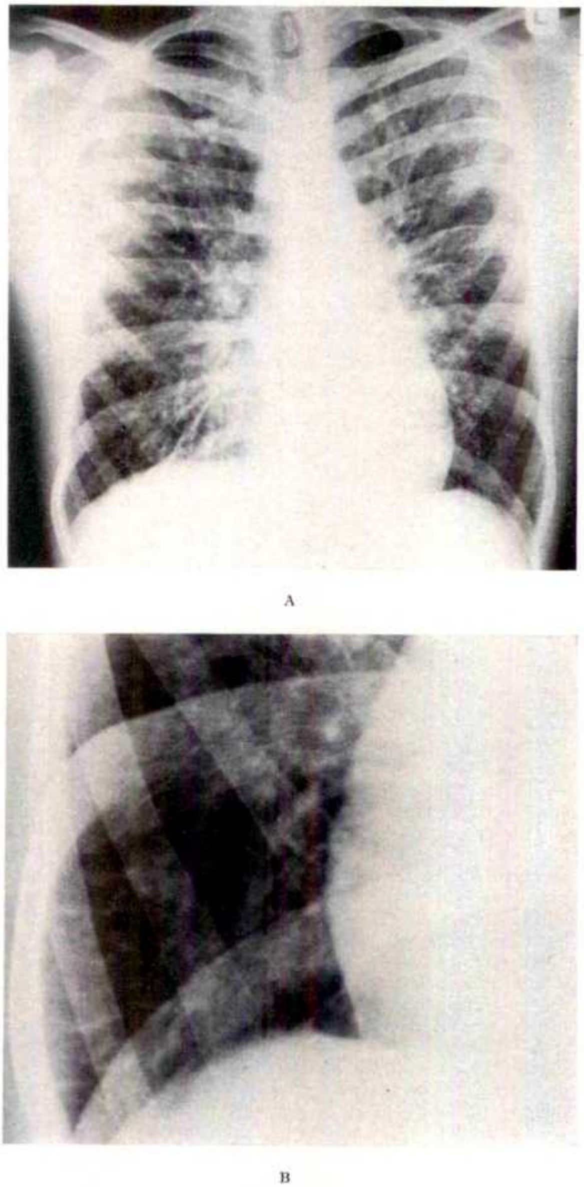

Fig. 1.

Chest radiograph on admission showing ill-defined opacities throughout both lung fields with well marked septal lines.

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Case reports

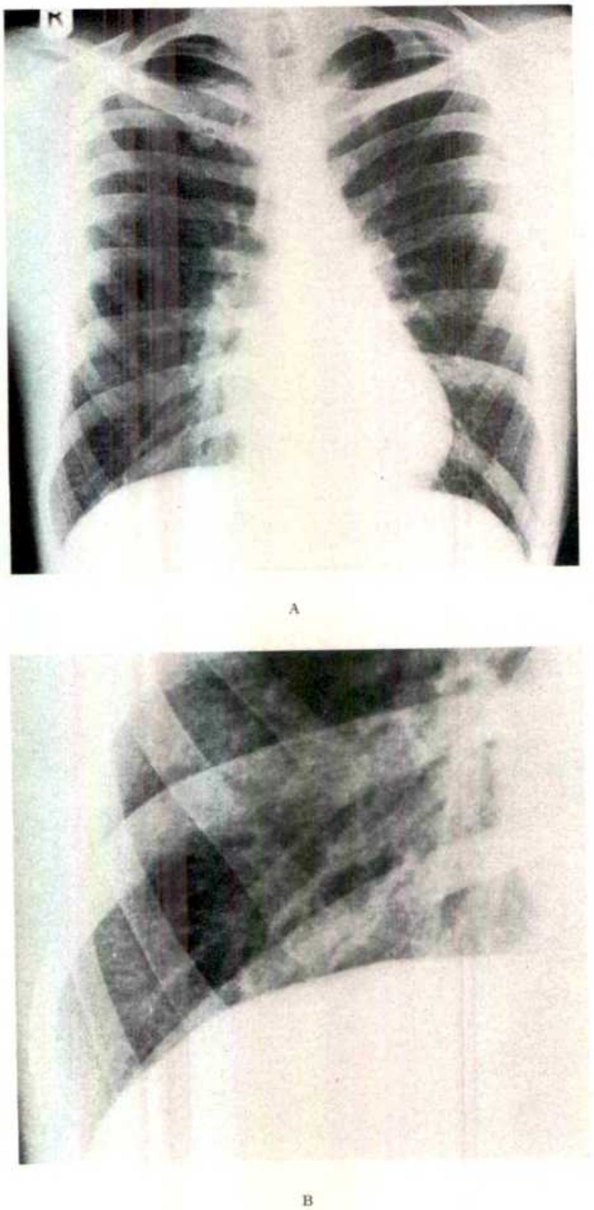

FIG. 2.

Chest radiograph following four days treatment with steroids showing complete clearing of the lung fields.

Nitrofurantoin. These authors believe that the radiological changes occurring after the administration of Nitrofurantoin are produced by an allergic transudate rather than by an inflammatory exudate, because of the rapid onset of the symptoms after the re-administration of the drug and the rapid improvement after the withdrawal of the drug. About half of the cases of Nitrofurantoin lung so far described have had a significant eosinophilia suggesting an allergic basis to the symptoms and radiographic appearances. In our case a blood eosinophil count of 14 per cent of 7,500 WBC was recorded, and we believe the appearance of the septal lines in this case, with rapid return to normality after treatment with steroids, is in favour of an allergic transudate into the interlobular septa.

ACKNOWLEDGMENTS

We are indebted to Dr. Peter Emerson for permission to publish this case.

REFERENCES

NGAN, H., MILLARD, R. J., LANT, A. F., and TRAPNELL, D. H., 1971. Nitrofurantoin lung. *The British Journal of Radiology*, *44*, 21–23.

TRAPNELL, D. H., 1973. The differential diagnosis of linear shadows in chest radiographs. *Radiologic Clinics of North America*, *11*, 77–92.

Intrapericardial barium in a case of peptic ulceration

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(*Received April, 1975 and in revised form July, 1975*)

Pneumopericardium is rare and is even more uncommon as a complication of benign gastric ulceration. Advances in surgical treatment for carcinoma of the oesophagus have led to more frequent thoracic interposition of the stomach for the resected portion of the oesophagus. The heterotopic stomach is liable to develop abnormalities similar to those which occur in the normally situated stomach. We report here a case in which pneumopericardium occurred following perforation of a benign gastric ulcer in a stomach that had been surgically advanced to the thorax following resection of a carcinoma of the oesophagus.

Case history

A female, born 1918, presented to the surgical clinic of St. Vincent's Hospital in 1960 complaining of dysphagia. Following admission and appropriate investigations, a diagnosis of carcinoma of the oesophagus was made. The stricture was surgically resected and the stomach brought up into the thorax and anastomosed with the upper portion of the oesophagus. Histological examination showed the presence of a well-differentiated squamous cell carcinoma which had partially penetrated the wall of the oesophagus. There was no vascular invasion and no involvement of lymph nodes by tumour. The patient's recovery was uneventful.

The patient remained well until February 1974, when she complained of severe pain, of six months' duration, in the left shoulder. Musculoskeletal and cardiac causes for the pain were investigated and none found. Following barium ingestion, a supine chest radiograph showed the appearances in Fig. 1. A horizontal ray radiograph of the chest in the supine position (Fig. 2) showed a crescentic outline of air in the pericardial sac. A lateral film (Fig. 3) showed barium posteriorly in the stomach entering the pericardium anteriorly. During this admission, the patient's condition deteriorated rapidly and she died within two days of the barium studies.

At autopsy, the main abnormal findings were seen within the thoracic cavity. The gastro-oesophageal anastomosis was intact. In the stomach, there was an ulcer, 4 cm in diameter, which had perforated anteriorly into the pericardium. Histology of the ulcer showed the features of benign peptic ulceration.

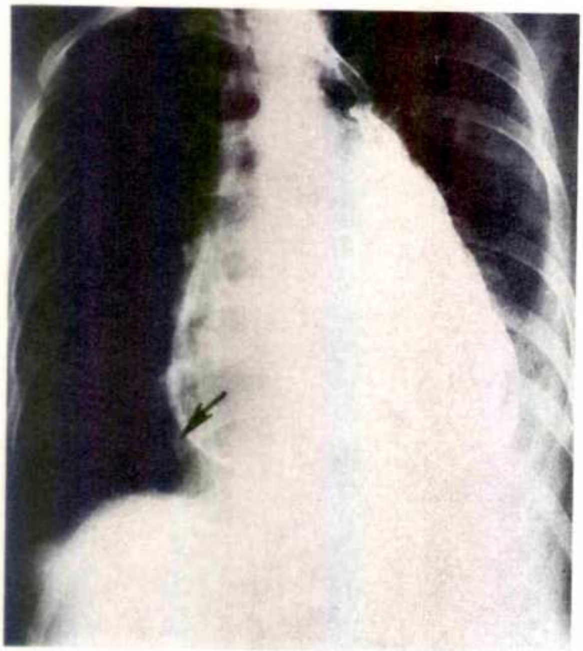

FIG. 1.

Supine chest radiograph after barium, showing intrathoracic stomach. Note thickened pericardium at right border (arrowed) of heart.

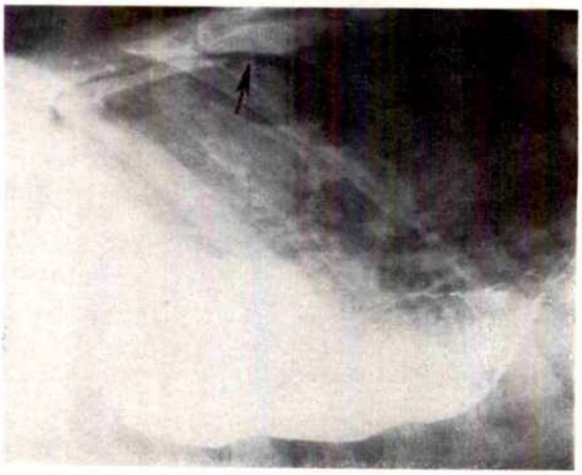

FIG. 2.

Horizontal ray radiograph of chest of patient in the supine position showing a crescentic outline (arrowed) of air in the pericardial sac.

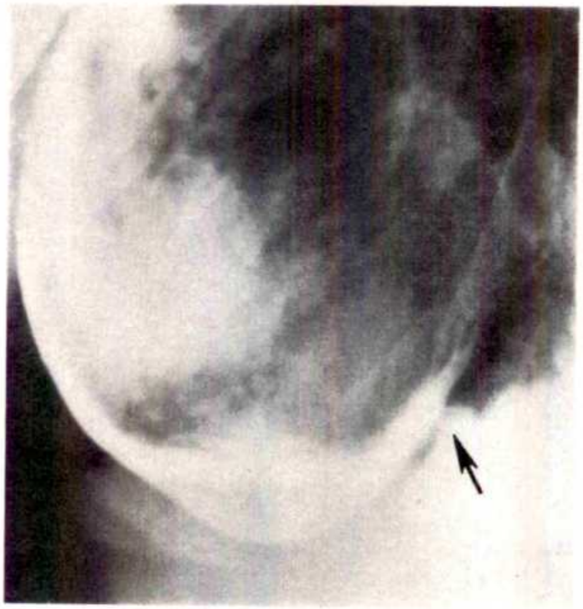

FIG. 3.

Lateral radiograph showing barium posteriorly in the stomach and entering the pericardium through fistula (arrowed).

DISCUSSION

The intrathoracic stomach, whether it is in the thorax as a result of surgery or because of hiatus hernia, may develop peptic ulceration. This peptic ulceration is subject to the complications, including perforation, of a peptic ulcer in any situation. However, because of its situation, perforation of the intrathoracic benign gastric ulcer may lead to unusual consequences.

Macarthur and Wright (1969) described five cases of benign chronic peptic ulceration occurring in the intrathoracic stomach in cases of hiatus hernia. Perforation occurred in four of these patients; no instance of perforation into the pericardium was seen.

Romhilt and Alexander (1965) described a case of pneumopericardium secondary to perforation of a benign gastric ulcer. Their patient had had a resection of a benign oesophageal stricture and gastro-oesophageal anastomosis three years before she presented. In their review of the literature they found ten cases in which a benign gastric ulcer had perforated into the pericardium. Nine of these ten cases had resulted from extension of a sub-diaphragmatic perforation. In the tenth case, the ulcer was situated in a hiatus hernia.

Romhilt and Alexander found their case to be unique in their perusal of the literature. We report a case showing several similar features but in which the perforation into the pericardium developed 14 years after a partial oesophagectomy for carcinoma of the oesophagus.

REFERENCES

MACARTHUR, A. M., and WRIGHT, J. E. C., 1969. Complications of intrathoracic gastric ulcer associated with hiatus hernia. *British Journal of Surgery*, *56*, 161–164.

ROMHILT, D. W., and ALEXANDER, J. W., 1965. Pneumopyopericardium secondary to perforation of benign gastric ulcer. *Journal of the American Medical Association*, *191*, 140–142.

Bone changes in intrahepatic biliary atresia

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(*Received April, 1975*)

The most frequent cause (60 per cent) of prolonged jaundice in infancy is biliary atresia (De Lorimier, 1973a). It is expected to occur once in every 20,000 to 30,000 births. Intrahepatic biliary atresia constitutes about 5 per cent of these cases, according to Schwartz (1974). A review of the radiologic literature failed to produce more than a dozen cases of intra hepatic biliary atresia with röntgen abnormalities. The purpose of this report is to emphasize the salient late röntgen changes seen in bones in patients with intrahepatic biliary atresia.

Case History

A three-and-a-half-year-old male was seen in the hospital clinic because of swelling of his feet, hands and knees. The previous history revealed that at two-and-a-half months of age he had been admitted to the hospital because of persistent jaundice. An exploratory laparotomy at that time showed the liver to be large, green and firm. The gall-bladder was hypoplastic. An operative cholangiogram had shown hypoplasia of the common-duct with abrupt stenosis at its junction with the liver, visualization of a single threadlike intrahepatic bile radical in the right lobe of the liver, and a non-patent cystic duct. Liver biopsy revealed severe bile stasis and periportal fibrosis. A diagnosis of intrahepatic biliary atresia was made. At this time and again at seven months of age, a bone survey was within normal limits. On his current admission a physical examination revealed a thin, malnourished boy with a distended abdomen. There was minimal tenderness over the anterior aspect of the knees and dorsum of the hands. The liver and spleen were palpable. Films of the skeleton showed the bones to be diffusely demineralized. There was cortical hyperostosis along the shafts of the long bones with marked soft-tissue swelling about the knees, ankles and wrists (Figs. 1 to 3). The metacarpal bones and phalanges were clubbed. The bone age was retarded, the skull was normal. The patient was in a remarkably good state of well-being.

DISCUSSION

Neonatal hepatitis, extrahepatic biliary atresia, choledochal cyst, and some cases of intrahepatic biliary atresia not associated with extrahepatic biliary atresia are felt to be secondary to an inflammatory response caused by prenatal and perinatal infection. The end result of this process is epithelial damage, periductal fibrosis and obliteration of the ducts (Landing, 1974). Viruses such as hepatitis and rubella have been incriminated as the most probable causative agents (Landing, 1974). Liver biopsies may be initially normal or show giant cell transformation and bile stasis. In later stages serial biopsies show the disappearance of portal and intralobular bile ducts (De Lorimier, 1973b). When intrahepatic biliary atresia results, a syndrome develops. Baker and Harris (1964) reviewed the clinical and radiographic features in intrahepatic biliary atresia. The pertinent clinical features include: severe jaundice,

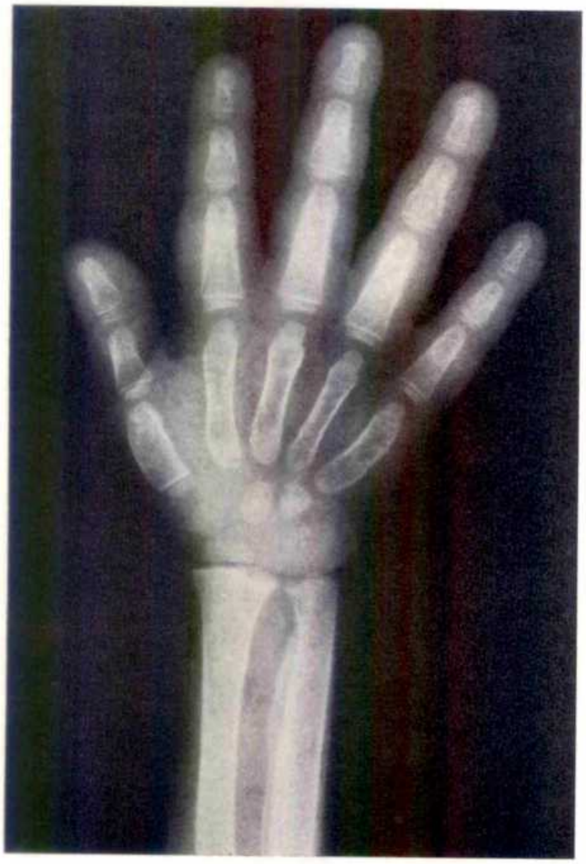

FIG. 1.

Radiograph of the left hand shows generalized demineralization of the bones with cortical hyperostosis in the distal ulna.

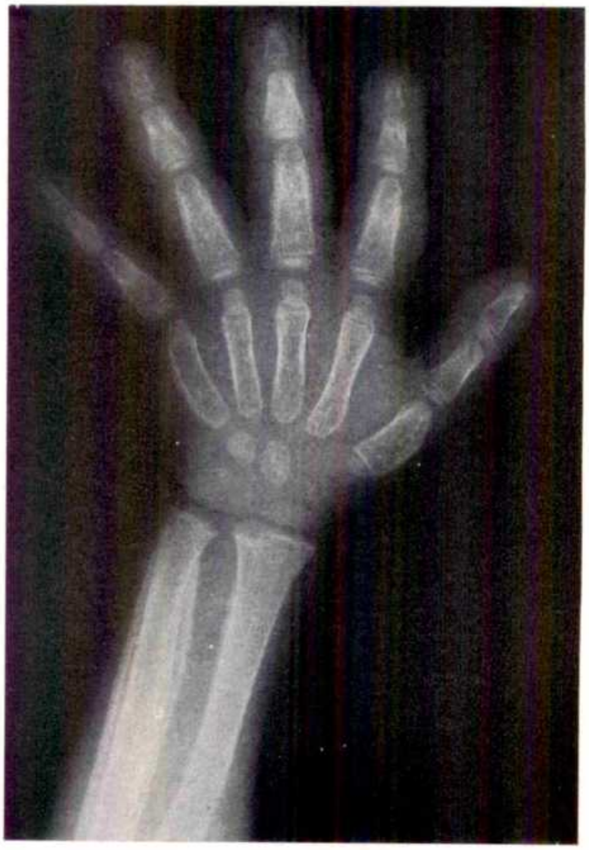

FIG. 2.

Cortical hyperostosis is especially evident in this radiograph of the right hand.

general debility, cutaneous xanthomata, a tendency to bleed, anaemia, portal hypertension and its sequelae.

Radiographically the bones do not show changes in the early stages of the disease. The skeleton becomes demineralized as the disease progresses. Stress fractures are common. There is thinning of the cortex with resorption of the primary trabeculae. The skeletal changes resemble those seen in many storage diseases. Another prominent radiographic feature is the cortical hyperostosis as exemplified by the case under discussion. This is felt by Baker and Harris (1964) to be secondary to subperiosteal bleeding. Bleeding also occurs into the extensor bursae. The metaphyses fail to show correct modelling (Baker and Harris, 1964). These patients may develop vitamin deficiency rickets.

Treatment is supportive. Liver transplantation may be of value in selected cases (Starzl, 1971).

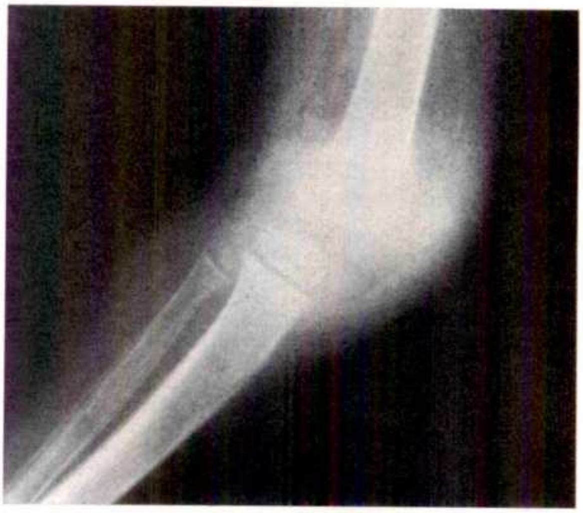

FIG. 3.

Radiograph of the right knee shows soft tissue swelling and extensive cortical hyperostosis.

1976, *British Journal of Radiology*, *49*, 181–183

REFERENCES

BAKER, D. H., and HARRIS, R. C., 1964. Congenital absence of the intrahepatic bile ducts. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 91*, 875–884.

DE LORIMIER, A. A., 1973a. Current concepts: surgical treatment of neonatal jaundice. *New England Journal of Medicine, 288*, 1284–1286.

1973b. *Current surgical diagnosis and treatment* pp., 1029 (Lange Medical Publishers, Los Altos).

LANDING, B. H., 1974. Considerations of the pathogenesis of neonatal hepatitis, biliary atresia and choledochal cyst: the concept of infantile obstructive cholangiopathy. *Progress in Pediatric Surgery, 6*, 113–139.

SCHWARTZ, S. I., 1974. *Principles of Surgery*, 2nd edn, pp. 1224 (McGraw-Hill, New York).

STARZL, T. E., 1971. The current status of liver transplantation. *Hospital Practice, 6*, 47–60.

Yersinia enterocolitica ileocolitis findings observed on barium examination

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(*Received March, 1975*)

In a surgically inviolate abdomen, the presence of right lower quandrant pain, accompanied by nausea and emesis, evokes strong consideration of appendicitis. Other entities, such as ureteric colic, ruptured duodenal ulcer, acute pelvic inflammatory disease, ovarian cyst torsion, ectopic pregnancy, acute gastroenteritis, or mesenteric adenitis also warrant consideration. Many of these may be excluded by clinical findings and appropriate laboratory studies. Exact identification of the offending organism is required in some inflammatory conditions, such as amoebiasis and salmonellosis. *Yersinia enterocolitica* is a gram-negative enteropathic organism found in the gastrointestinal tract of humans; it can produce acute ileocolitis and a clinical syndrome virtually indistinguishable from acute appendicitis (Weber, Finlayson and Mark, 1970). Yersinia ileocolitis can only be conclusively diagnosed by identification of the Yersinia organism. The radiologist can suggest the possibility of Yersinia ileocolitis so that appropriate evaluation will follow. The following is a case report of *Yersinia enterocolitica* induced ileocolitis with barium examination of the colon.

Case history

A 26-year-old woman had acute onset of nausea, diarrhoea, and pain in the right lower quadrant of the abdomen. Twenty-four hours after the onset of symptoms, the patient entered the hospital emergency-room. Physical examination disclosed the presence of fever and a tense abdomen. Specific tenderness was elicited in the area of McBurney's point and peritoneal irritation was indicated by the presence of rebound tenderness. On digital examination the rectum was painful on the right side.

Laboratory studies were unremarkable, except for elevated white blood cell count (18,600/mm^3) with predominance of polymorphonuclear neutrophils. At surgical exploration, the serosal coverings of the ileum and adjacent caecum were found to be erythematous. The bowel and the adjoining mesentery were oedematous; lymph-nodes in the adjacent area were enlarged. The appendix was removed and inversion of the appendiceal stump was performed. On pathological examination, the appendix was considered normal, but it was not cultured for pathogenic organisms.

Following surgery, the patient continued to experience right lower quadrant pain and diarrhoea. Twelve days after surgery, serum was drawn for reactivity to Yersinia antigen. At this time, with the possibility of regional enteritis being entertained, the patient was subjected to barium examination of the small bowel. Abnormal findings were observed in the caecum and distal ileum (Fig. 1A and B).

Following initial barium study, the patient began to improve, and within one month she was asymptomatic. Serum was drawn (28 days after surgery) for reactivity to Yersinia antigen. A repeat barium enema was interpreted as normal. Comparison of paired serum titers demonstrated a fourfold difference in reactivity to *Yersinia enterocolitica*, Type II.

DISCUSSION

Yersinia, a gram-negative coccoid organism, was initially isolated in 1883 from a tuberculous forearm lesion in a child who died of meningitis. The organism was subsequently designated *Yersinia pseudotuberculosis* after being observed as a frequent pathogen in guinea pigs used for tuberculosis research (Mair, 1965). Initially part of the genus Pasteurella, recent taxonomic revision has established the classification of Yersinia with inclusion of *Yersinia pseudotuberculosis* and closely related *Yersinia enterocolitica* (Nilehn, 1967; Smith and Thal, 1965).

Yersinia has been frequently cultured from faecal material of rodents, birds, monkeys and sheep. It is not found in man as a normal commensal bowel inhabitant. Identification of this organism can be difficult. It is frequently confused with certain enterobacteriaceae, *i.e.* "atypical coliforms", and misdiagnosed. Selected bacteriologic reactions allow differentiation of this organism from other enteric pathogens (Sonnenwirth, 1970). Both *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* have pathogenic potential for man. In humans, the organism has a proclivity for causing gastro-enteritis. Small outbreaks of Yersinia-related gastro-enteritis have been reported in United States literature (Gutman *et al.*, 1973).

Initially, reported as a human pathogen in the United States by Schleifstein and Coleman (1939), this organism received little attention in this country until later. In 1958, Knapp reported that some cases of mesenteric adenitis were related to *Yersinia pseudotuberculosis*. In instances of enteritis secondary to Yersinia, patients generally present with various somatic signs and symptoms including fever, lethargy, pharyngitis, diarrhoea, and abdominal pain. Instances of right lower quadrant pain, fever, leukocytosis and a mass on rectal examination have prompted the diagnosis of appendicitis and subsequent appendectomy. In most patients, resolution of the diarrhoea and fever has occurred spontaneously, although frequently resolution of the symptoms may be slow (Brzin, 1968; Gutman *et al.*, 1973). Route of disease transmission is probably faecal-oral from an infected source—food, animal or another person (Ahvonen, 1972).

The diagnosis of Yersinia ileocolitis may be made by stool culture, culture of mesenteric nodes, or indirectly by paired serum samples for agglutinin titers. A four-fold change in agglutinin titers is generally considered diagnostic of the disease (Gutman *et al.*, 1973). Yersinia infection is usually self-limited and not treated by antimicrobial agents unless sepsis or prolonged elevation of serologic titers is present. The Yersinia organism is sensitive to various antibiotic preparations, including ampicillin, kanamycin, and tetracycline (Brzin, 1968).

Specific findings on barium studies of the colon have been made in respect to appendicitis, including nonfilling of the appendiceal lumen and presence of mass adjacent to the caecum (Sorter, 1973). In the case presented, röntgen findings consisted of spasm and bowel wall thickening involving the proximal right colon and adjacent distal ileum. These findings are nonspecific and could be simulated by a number of acute inflammatory processes, including amoebiasis, salmonellosis, and acute regional enteritis.

Radiological studies in the case presented showed findings consistent with an inflammatory process of the ileocaecal area. The radiologist has a role in

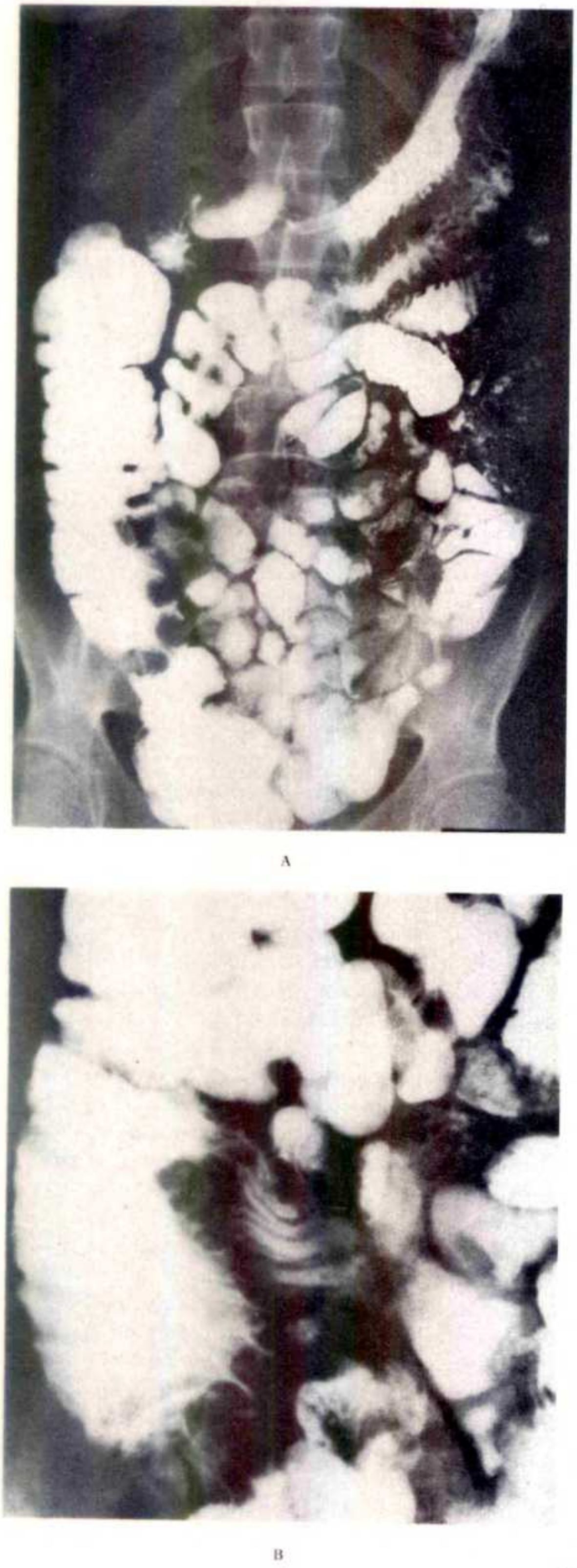

FIG. 1.

(A) Small bowel examination. Irregular narrowing of the proximal right colon, especially medial wall. There is some question of fistulous communication of small bowel to the colon.

(B) Medial border of caecum spiculated with considerable separation between adjacent bowel loops. The separation is considered a reflection of bowel wall oedema.

suggesting Yersinia ileocolitis so that it may be identified by laboratory methods currently available. In the subacute state, Yersinia ileocolitis should be distinguished from regional enteritis since both disease processes can initially be similar.

ACKNOWLEDGEMENT

Serologic studies were performed by the California State Department of Public Health, Microbial Diseases Laboratory, Berkeley, California.

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

REFERENCES

AHVONEN, P., 1972. Human yersiniosis in Finland: II. Clinical features. *Annals of Clinical Research*, *4*, 39–48.

BRZIN, B., 1968. The influence of antibiotics and cytostatics on the morphology of "Pasteurella pseudotuberculosis" and "Yersinia enterocolitica". In *Symposia Series in Immunological Standardization: International Symposium on Pseudotuberculosis*, ed. R. H. Regamey pp.207–210. (*Basel, S. Karger*,)

GUTMAN, L. T., OTTESEN, E. A., QUAN, T. J., NOCE, P. S., and KATZ, S. L., 1973. An inter-familial out-break of *Yersinia enterocolitica* enteritis. *New England Journal of Medicine*, *288*, 1372–1377.

KNAPP, W., 1958. Mesenteric adenitis due to *Pasteurella pseudotuberculosis* in young people. *New England Journal of Medicine*, *259*, 776—778.

MAIR, N. S., 1965. Sources and serological classification of 177 strains of *Pasteurella pseudotuberculosis* isolated in Great Britain. *Journal of Pathology*, *90*, 275–278.

NILEHN, B., 1967. Studies on *Yersinia enterocolitica*: characterization of 28 strains from human and animal sources. *Acta Pathologica et Microbiologica Scandinavica*, *69*, 83–91.

SCHLEIFSTEIN, J. I., and COLEMAN, M. B., 1939. An unidentified micro-organism resembling *B. lingnieri*, and *Past. pseudotuberculosis*, and pathogenic for man. *New York State Journal of Medicine*, *39*, 1749–1753.

SMITH, J., and THAL, E., 1965. A taxonomic study of genus Pasteurella using a numerical technique. *Acta Pathologica et Microbiologica Scandinavica*, *64*, 213–223.

SONNENWIRTH, A. C., 1970. Gram negative bacilli, vibrios and spirilla. In *Gradwohl's Clinical Laboratory Methods and Diagnosis. A Textbook on Laboratory procedures and their interpretation*, 7th edn, Eds. S. Frankel, S. Reitman, and A. C. Sonnenwirth, pp. 1275–1282 (Mosby, St Louis).

SORTER, C. S., 1973. The contribution of the radiologist to the diagnosis of acute appendicitis. *Seminars in Roentgenology*, *8*, 375–388.

WEBER, J., FINLAYSON, N. B., and MARK, J. B. D., 1970. Mesenteric lymphadenitis and terminal ileitis due to *Yersinia pseudotuberculosis*. *New England Journal of Medicine*, *283*, 172–174.

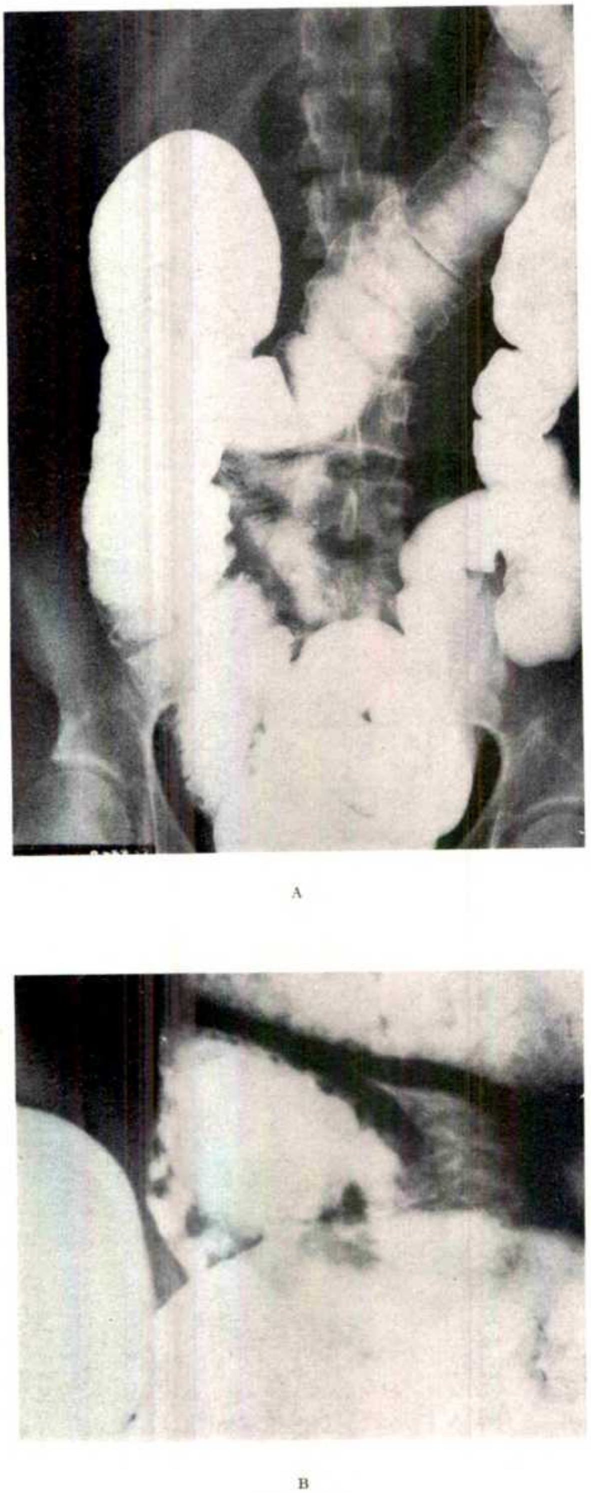

FIG. 2.

(A) Barium colon study reveals well distended proximal right colon with no contour abnormalities.

(B) Normal appearing ileocaecal valve and distal ileum.

1976, *British Journal of Radiology*, 49, 184–185

Case reports

Hepatic haematoma in polyarteritis nodosa

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(*Received December, 1974 and in revised form March, 1975*)

Case history

A 21-year-old man presented two years ago with upper abdominal discomfort, anorexia, weight loss and low grade fever. He was hypertensive and had a right foot drop and hepatosplenomegaly. Polyarteritis nodosa was diagnosed on muscle biopsy but a liver biopsy was normal. Regression of symptoms followed treatment with corticosteroids and methyldopa.

In 1974, whilst in hospital for treatment of Vincent's angina, he suddenly became shocked with upper abdominal pain. His liver became enlarged and tender. Transfusion produced a rapid recovery. The following day a liver scan was performed (Fig. 1). A week later he suffered a similar episode requiring further transfusion.

Abdominal angiography was then performed and demonstrated the changes of polyarteritis nodosa in the liver (Figs. 2–3) without other visceral involvement.

DISCUSSION

It is well known that polyarteritis nodosa may affect the parenchymal arteries of many viscera but particularly those in the abdomen. However, it was not

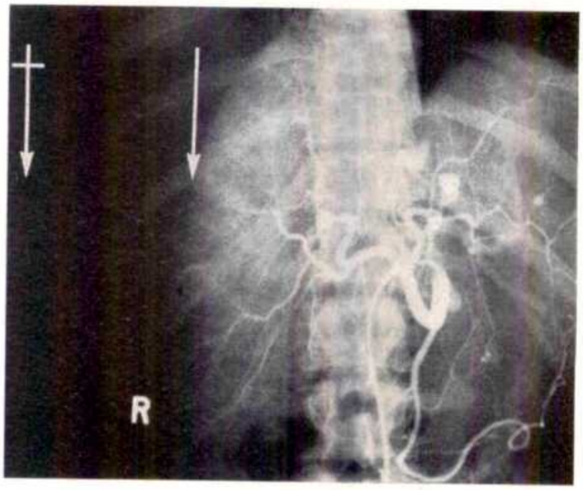

FIG. 2.

Selective hepatic arteriogram—antero-posterior.

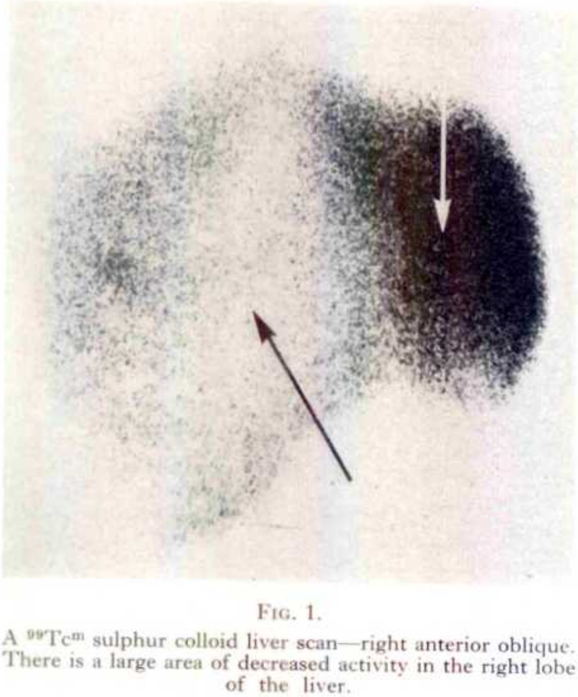

FIG. 1.

A ^{99}Tc^{m} sulphur colloid liver scan—right anterior oblique. There is a large area of decreased activity in the right lobe of the liver.

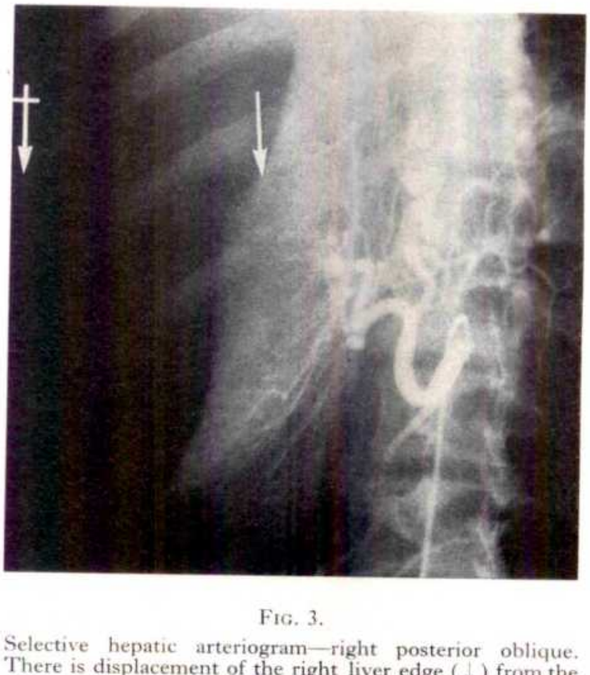

FIG. 3.

Selective hepatic arteriogram—right posterior oblique. There is displacement of the right liver edge (↓) from the abdominal wall (↧) and displacement of the coeliac axis to the left. Many aneurysms and stenoses are demonstrated in the intraparenchymal arteries. Some of the aneurysms are large and multilocular.

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until 1965 that the ante-mortem angiographic findings were demonstrated (Fleming and Stern, 1965; Bron, Strott and Shapiro, 1965). Since then abdominal arteriography has been used in both diagnosis and management based on the high frequency of pathological changes found in the abdominal viscera. Muscle biopsy is commonly used in the investigation of these patients but voluntary muscle is affected in only 20–39 per cent of cases whereas renal involvement is described in 80–85 per cent (Cabal and Holtz, 1971).

Most reported cases of polyarteritis nodosa, studied by angiography, have demonstrated renal involvement but similar changes are described in hepatic, splenic, mesenteric, lumbar, intercostal, pulmonary and intracerebral arteries (Herschmann, Blumm and Lee, 1970; Leonhardt, Jakobson and Ringqvist, 1972). Haemorrhage from affected arteries is well recognized and many cases of perinephric haematoma are described (Ostrum and Soder, 1960; Peterson *et al.*, 1970). Haemorrhage may also occur from mesenteric arteries (Capps and Klein, 1970).

The aneurysms described in polyarteritis nodosa are usually small, but larger aneurysms have been described in the hepatic arteries (Chudácek, 1967; Essinger and Bonard, 1971) even in the presence of a normal liver biopsy (Bron and Gajaraj, 1970). Robins and Bookstein (1972) have reported regression of aneurysms during treatment. The angiographic appearances are distinctive, but not pathognomonic as they have also been described in the necrotizing arteritis associated with drug abuse (Halpern and Citron, 1971).

The present case demonstrates widespread hepatic abnormalities, without renal or other abdominal visceral involvement. Some of the aneurysms are large and multilocular. The clinical, liver scan and angiographic evidence also suggests that the patient suffered massive hepatic haemorrhage on at least two occasions—firstly into the central portion right lobe and subsequently into the outer part of the right lobe with displacement of the rest of the liver substance to the left. The haematoma appears to have been contained within the liver capsule and was limited superiorly by the liver's attachment to the central tendon of the diaphragm. At no time was there clinical or radiological evidence of free intraperitoneal blood.

Angiography has been valuable in demonstrating the limitation of visceral involvement and should a further hepatic bleed occur ligation of the common hepatic artery will be seriously considered.

This case has also been presented to the Clinical Section of the Royal Society of Medicine (Proceedings of the Royal Society of Medicine, 1976, in press).

ACKNOWLEDGMENTS

We are grateful to Dr. C. M. Oakley for permission to publish this case.

REFERENCES

BRON, K. M., and GAJARAJ, A., 1970. Demonstration of hepatic aneurysms in polyarteritis nodosa by arteriography. *New England Journal of Medicine, 282*, 1024–1025

BRON, K. M., STROTT, C. A., and SHAPIRO, A. P., 1965. The diagnostic value of angiographic observations in polyarteritis nodosa. A case of multiple aneurysms in, the visceral organs. *Archives of Internal Medicine, 116* 450–454.

CABAL E., and HOLTZ, S., 1971. Polyarteritis as a cause of intestinal haemorrhage. *Gastroenterology, 61*, 99–105.

CAPPS, J. H., and KLEIN, R. M., 1970. Polyarteritis nodosa as a cause of perirenal and retroperitoneal haemorrhage. *Radiology, 94*, 143–146.

CHUDÁCEK, Z., 1967. Angiographic diagnosis of polyarteritis nodosa of the liver, kidney and mesentery. *British Journal of Radiology, 40*, 864–865.

ESSINGER, A., and BONARD, M., 1971. Panarteritis nodosa, an angiographic entity—presentation of two cases. *British Journal of Radiology, 44*, 184–188.

FLEMING, R. J., and STERN, L. Z., 1965. Multiple intraparenchymal renal aneurysms in polyarteritis nodosa. *Radiology, 84*, 100–103.

HALPERN, M., and CITRON, B. P., 1971. Necrotizing angiitis associated with drug abuse. *American Journal of Roentgenology, 111*, 663–671.

HERSCHMAN, A., BLUM, R., and LEE, Y. C., 1970. Angiographic findings in polyarteritis nodosa. *Radiology, 94*, 147–148.

LEONHARDT, E. T. G., JAKOBSON, H., and RINGQVIST, O. T. A., 1972. Angiographic and clinico-physiologic investigation of a case of polyarteritis nodosa. *American Journal of Medicine, 53*, 242–256.

OSTRUM, B. J., and SODER, P. D., 1960. Periarteritis nodosa complicated by spontaneous haematoma; Roentgenographic findings in 3 cases and review of the literature. *American Journal of Roentgenology, 84*, 849–860.

PETERSON, C., WILLERSON, J. T., DOPPMAN, J. L., and DECKER, J. L., 1970. Polyarteritis nodosa with bilateral renal artery aneurysms and perirenal haematomas; angiographic and nephrotomographic features. *British Journal of Radiology, 43*, 62–71.

ROBINS, J. M., and BOOKSTEIN, J. J., 1972. Regressing aneurysms in periarteritis nodosa. *Radiology, 104*, 39–42.

1976, *British Journal of Radiology*, *49*, 186–187

Case reports

Milk of calcium of the adrenal gland

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(*Received February, 1975*)

Milk of calcium is found most frequently in the gall-bladder and biliary tract (Kornblum and Hall, 1935; Simmonds, 1957), uncommonly in renal pyelogenic cysts (Murray, 1971; Berg, 1967) and rarely in pancreatic pseudocysts (Van Nostrand, Renert and Hileman, 1974). Recently milk of calcium was observed in an adrenal gland cyst. Liquid calcification has not been previously documented in the adrenal gland.

Case history

M.R., a 37-year-old man, presented with vague abdominal pain of several months' duration. Physical examination was normal. Laboratory examination demonstrated a normal blood count, serum lipase, serum amylase, SGOT, alkaline phosphatase, creatinine, calcium and phosphorus. Chest radiography was normal. An abdominal radiograph done in the erect position revealed a partially calcified left upper quadrant cystic mass which contained a crescent-shaped calcium density (Fig. 1). An upright lateral film demonstrated the mass to overlay the spine (Fig. 2). An excretory urogram placed the mass outside of the kidney in the region of the adrenal (Fig. 3). There was no evidence of renal or urinary tract disease. A complete endocrine profile was within normal limits.

On the sixth hospital day the patient underwent an exploratory laporotomy which revealed a 7 cm cystic mass involving the lateral two-thirds of the left adrenal gland. The medial third of the adrenal gland was normal. A total left adrenalectomy was performed, and a multicystic mass weighing 28 grams was removed. The overall mass measured 8 × 4·5 × 3 cm, while the largest cystic cavity was 4·5 cm in diameter. Upon cutting the cyst wall, a pearly-white putty-like material with a gritty consistency and 3–4 cm^3 of a cloudy, viscous fluid was removed. Microscopic examination revealed multiloculated cysts lined by endothelium and containing a mixture of eosinophilic protein material, foci of calcification and red cells. There was no evidence of malignancy or inflammation. The diagnosis was that of an angiomatous adrenal cyst containing milk of calcium.

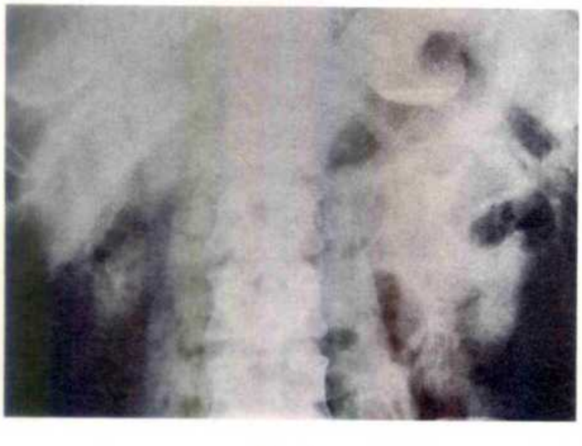

FIG. 1.

Upright radiograph of the abdomen demonstrating cystic structure in left upper abdomen containing a crescent-shaped calcium density.

DISCUSSION

Calcification of the adrenal gland occurs in a variety of disease entities, but recent reviews (Martin, 1965; McAlister and Koehler, 1967, and McAlister and Lester, 1971) have failed to report any instances of milk of calcium occurring in the

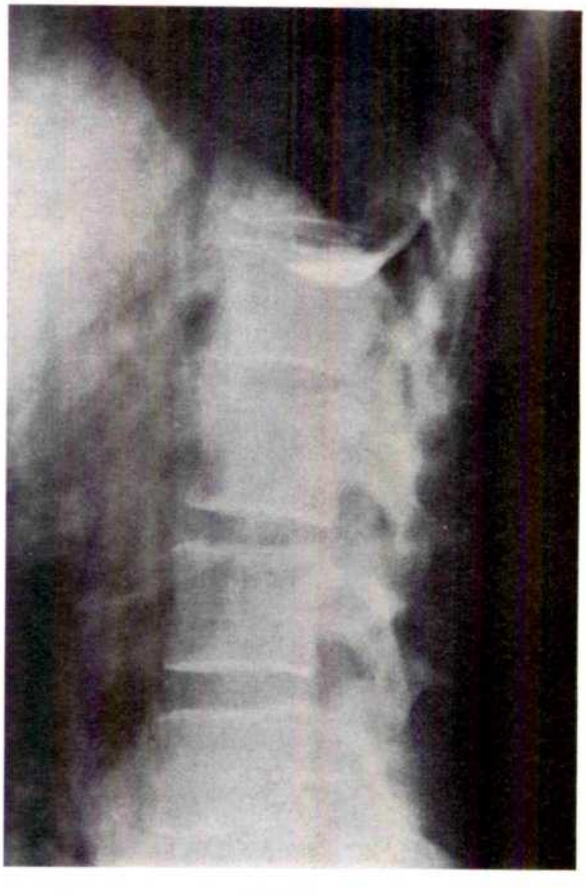

FIG. 2.

An upright lateral abdomen radiograph showing the cystic mass to overlay the spine.

adrenal gland. Collections of milk of calcium which occur in the gall-bladder are most often associated with cystic duct obstruction secondary to cholelithiasis and chronic cholecystitis (Knutsson, 1933). Chemical analysis has shown calcium carbonate to be the predominant component of milk of calcium (Walker, 1960) and calcium carbonate has been found to be deposited in the wall of the gall-bladder as well as excreted into the lumen.

Renal milk of calcium is usually a fortuitous finding in normally functioning kidneys (Murray, 1971). It is usually located in pyelogenic cysts and obstruction of drainage has been proposed (Murray, 1971; Berg, 1967), but not proved to play a role in the formation of milk of calcium in the kidney.

A recent case report documented milk of calcium occurring within a pancreatic pseudocyst (Van Nostrand *et al.*, 1974). The author postulated the walled-off pseudocyst produced a condition analogous to the chronically inflammed gall-bladder with cystic-duct obstruction. Van Nostrand postulated that milk of calcium then was deposited within the pseudocyst much like that found in the gall-bladder (Van Nostrand *et al.*, 1974).

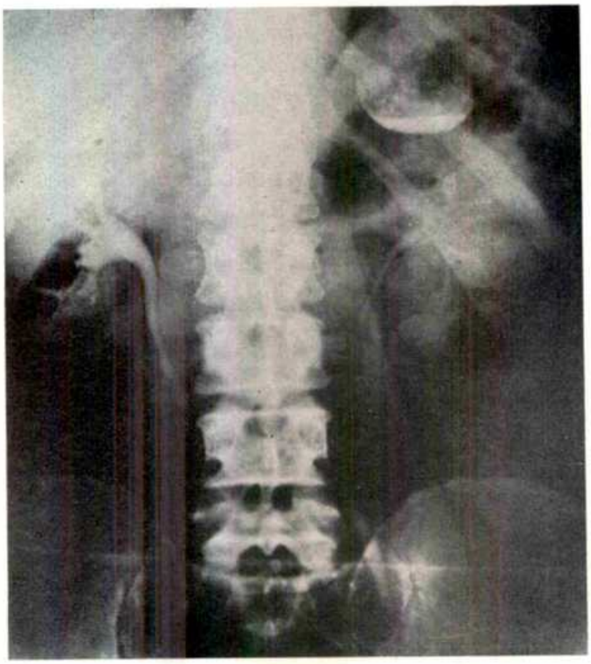

FIG. 3.

An excretory urogram demonstrating the cystic mass to be suprarenal in location and located in the region of the left adrenal gland.

The aetiology and pathogenesis of milk of calcium collections remain unknown. A cystic structure with impaired or obstructed drainage is common to all locations where milk of calcium has been found. Chronic inflammation or haemorrhage may play a role in the secretion of calcium into these cystic structures.

The patient herein reported had an angiomatous adrenal cyst which was walled off and contained milk of calcium. A history of infection or trauma was lacking. There was no drainage of the cyst and calcium was deposited in the walls of the cyst as well as within the contents.

REFERENCES

BERG, R. A., 1967. Milk of calcium renal disease: report of cases and review of literature. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 101,* 708–713.

KNUTSSON, F., 1933. On limy bile. *Acta Radiologica, 14,* 453–462.

KORNBLUM, K., and HALL, W. C., 1935, Roentgenologic significance of "milk of calcium" bile. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 33,* 611–623.

MCALISTER, W. H., and KOEHLER, P. R., 1967. Diseases of the adrenal. *Radiologic Clinics of North America, 5,* 205–220.

MCALISTER, W. H., and LESTER, P. D., 1971. Disease of the adrenal. *Medical Radiology and Photography, 47,* 62–81.

MARTIN, J. F., 1965. Suprarenal calcification. *Radiologic Clinics of North America, 3,* 129–138.

MURRAY, R. L., 1971. Milk of calcium in the kidney: diagnostic features on vertical beam roentgenograms. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 113,* 445–459.

SIMMONDS, H. T., 1957. Milk of calcium bile in the common duct. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 78,* 1020–1023.

VAN NOSTRAND, W. R., RENERT, W. A., and HILEMAN, W. T., 1974. Milk of calcium of the pancreas. *Radiology, 110,* 323–324.

WALKER, W. H., PEARSON, R. E., and JOHNSON, N. R., 1960. Milk of calcium renal stone. *Journal of Urology, 84,* 517–520.

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Case reports

Congenital diverticulum of the right ventricle: clinical and angiographic features

By C. B. Higgins, M.D., W. G. Hayden, M.D., J. Copeland, M.D., and E. B. Stinson, M.D.

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(*Received July, 1975*)

Congenital ventricular diverticula are exceedingly rare and usually accompanied by other cardiac anomalies. A number of left ventricular diverticula have been reported in association with midline defects in the pericardium, diaphragm and anterior abdominal wall (Cantrell, Haller and Ravitch, 1958; Edgett *et al.*, 1969), and as an isolated lesion in natives of geographically localized areas of Africa (Chesler *et al.*, 1965; Lurie, 1960) and sporadically from elsewhere (Dimich *et al.*, 1969; Paronetto and Strauss, 1963; Treistman *et al.*, 1973). Few descriptions of right ventricular diverticula are available (Carter *et al.*, 1971; Cumming, 1969). The current case report depicts the angiographic features of a contractile diverticulum of the right ventricle, which may have been the origin of two large pulmonary emboli.

Case history

The patient, a ten-year-old caucasian boy, was found to have a systolic cardiac murmur at age six months. Although asymptomatic at that time, there was radiographic evidence of increased pulmonary blood flow. Cardiac catheterization at age six years while he was still asymptomatic revealed a high membranous ventricular septal defect with direct shunting from the left ventricle to right atrium. In addition, a right ventricular cine-angiogram demonstrated a diverticulum projecting from the base of the right ventricular outflow tract.

At age nine years he developed an episode of subacute bacterial endocarditis apparently involving the right side of the heart; *a* streptococcus was shown to be the responsible organism. The illness was complicated by large pulmonary emboli to the right middle lobe and a day later to the right lower lobe.

At age ten he was admitted for a second cardiac catheterization which demonstrated normal pressure in all cardiac chambers and a high membranous ventricular septal defect with a pulmonary to systemic flow ratio of 1·6:1. A biplane right ventricular cine-angiogram in the left anterior oblique projection again demonstrated the broad-necked diverticulum attached to the right anterolateral aspect of the infundibulum (Figs. 1 and 2). The diverticulum had a trabecular pattern and contraction identical to the remainder of the right ventricle (Figs. 1 and 2). A muscular diverticulum which contracted synchronously with the remainder of the right ventricle was observed at the time of operative closure of the ventricular septal defect.

Discussion

The right ventricular diverticulum described in the above case report is to our knowledge only the fourth such diverticulum recorded in the English literature (Carter *et al.*, 1971; Cumming, 1969). Cumming (1969) described a nine-year-old boy with an atrial septal defect and a small outpocketing from the apex of the right ventricle which at autopsy was found to be composed entirely of fibrous tissue. Two cases of congenital diverticulum located at the base of the right ventricle in association with tetralogy of Fallot and double outlet right ventricle bear a closer resemblance to the diverticulum in the current report (Carter *et al.*, 1971). It is of interest that associated cardiac anomalies were present in each of the three previously-reported cases as well as in the current case.

Angiographic features peculiar to the current case were the distinct trabecular pattern nearly identical to that present throughout the right ventricular chamber and contractions synchronous with the remainder of the right ventricle. These findings when present, allow differentiation from an acquired ventricular aneurysm and an enlarged right atrial appendage which lack these two features. However, the diverticulum was devoid of a normal trabecular pattern in two of the previously described cases (Carter *et al.*, 1971; Cumming, 1969). Moreover, the two cases in which selective right ventricular cine-angiograms were available demonstrated paradoxical expansion of the diverticulum during ventricular systole (Carter *et al.*, 1971; Cumming, 1969). The appearance of a normal trabecular and contractile pattern in the current case suggests that the diverticulum arises as a consequence of an accessory outpocketing developing from the primitive ventricle.

The rare but more frequently encountered left ventricular diverticula arise from the apex of the heart in association with midline truncal musculo-skeletal defects (Cantrell *et al.*, 1958; Edgett *et al.*, 1969). Other types of congenital outpouchings from the left ventricle are the isolated congenital outpouchings from the left ventricular apex or sub-valvular area of the left ventricle which have been not infrequently encountered in geographically localized areas of Africa (Chesler *et al.*, 1965; Chesler, Tucker and Barlow, 1967; Lurie, 1960), and more rarely from other areas (Dimich, 1969;

Paronetto and Strauss, 1963; Triestman *et al.*, 1973). The latter lesions are more properly termed congenital aneurysms since their walls are composed entirely of fibrous tissue and they expand paradoxically during ventricular systole.

The occurrence of subacute bacterial endocarditis and pulmonary embolism in the current case is noteworthy since there are reports of bacterial endocarditis (Chesler *et al.*, 1965) and systemic emboli

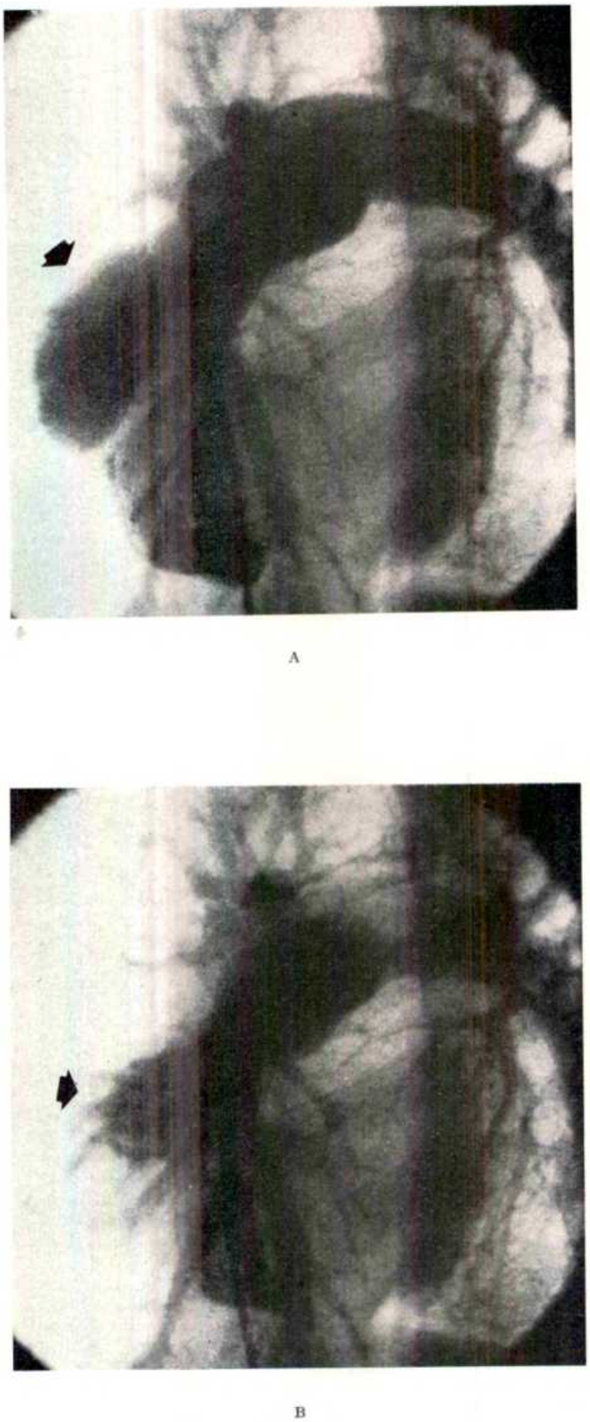

FIG. 1.

Cine-angiocardiogram in the LAO projection demonstrated the diverticulum arising from the proximal portion of the right ventricular outflow tract in diastole (A) and systole (B). Note that the contractile pattern of the diverticulum is synchronous with that of the remainder of the right ventricle. Diverticulum (arrow).

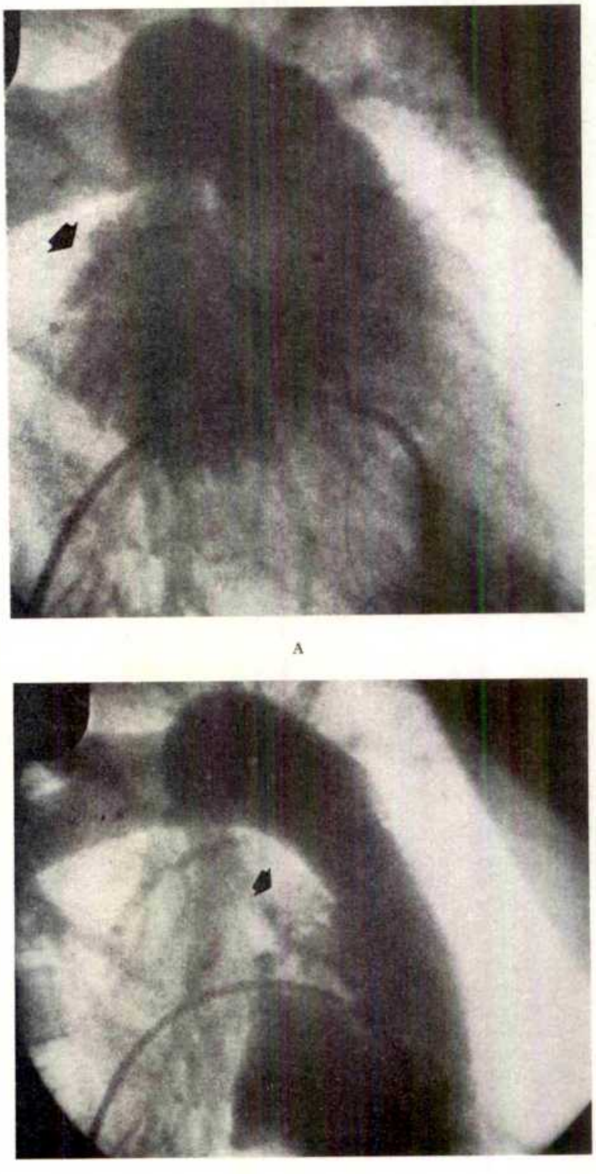

FIG. 2.

Cine-angiocardiogram in the RAO projection shows the substantial variation in size of the diverticulum in diastole (A) and systole (B). Diverticulum (arrow).

(Chesler *et al.*, 1967) arising from congenital left ventricular diverticula. This observation suggests that while a normally contracting right ventricular diverticulum appears to be haemodynamically innocuous, it may be a focus for the deposit of bacteria or the formation of intracardiac thrombus.

REFERENCES

CANTRELL, J. R., HALLER, J. A., and RAVITCH, M. M., 1958. A syndrome of congenital defects involving the abdominal wall, sternum, diaphragm, pericardium and heart. *Surgery, Gynecology and Obstetrics*, *107*, 602–614.

CARTER, J. B., VAN TASSEL, R. A., MOLLER, J. H., AMPLATZ, K., and EDWARDS, J. E., 1971. Congenital diverticulum of the right ventricle. Association with pulmonary stenosis and ventricular septal defect. *American Journal of Cardiology*, *28*, 478–482.

CHESLER, E., JOFFE, N., SCHAMROTH, L., and MEYERS, A., 1965. Annular subvalvular left ventricular aneurysms in the South African Bantu. *Circulation*, *32*, 43–51.

CHESLER, E., TUCHER, R. B. K., and BARLOW, J. B., 1967. Subvalvular and apical left ventricular aneurysms in the Bantu as a source of systemic emboli. *Circulation*, *35*, 1156–1162.

CUMMING, G. R., 1969. Congenital diverticulum of the right ventricle. *American Journal of Cardiology*, *23*, 294–297.

DIMICH, I., STEINFELD, L., BARON, M., and GOLDSHLAGER, A., 1969. Calcified left ventricular aneurysm in children. *American Journal of Cardiology*, *23*, 739–743.

EDGETT, J. W., NELSON, W. P., HALL, R. J., FISHBACK, M. E., and JAHNKE, E. J., 1969. Diverticulum of the heart. Part of the syndrome of congenital cardiac and midline thoracic and abdominal defects. *American Journal of Cardiology*, *24*, 580–583.

LURIE, A. O., 1960. Left ventricular aneurysm in the African. *British Heart Journal*, *22*, 181–188.

PARONETTO, F., and STRAUSS, L., 1963. Aneurysm of the left ventricle due to congenital muscle defects in an infant. *American Journal of Cardiology*, *12*, 721–729.

TREISTMAN, B., COOLEY, D. A., LUFSCHANOWSKI, R., and LEACHMAN, R. D., 1973. Diverticulum or aneurysm of left ventricle. *American Journal of Cardiology*, *32*, 119–123.

Obituary

John Mitchell

The death occurred on Monday, July 21, 1975, of Dr. John Mitchell, M.B., Ch.B., D.M.R.D., Consultant Radiologist to the Chesterfield Royal Hospital. He was 47.

Born in London, John trained and qualified at Leeds Medical School. After military service, one of his hospital posts was as Casualty Officer in Chesterfield Royal Hospital; it is recalled that he was a very good house-surgeon.

He trained in radiology in Sheffield, and then became Registrar and Senior Registrar at the Northern General Hospital where he enjoyed the full confidence and became the close friend of the consultant radiologists (the late Dr. E. K. Abbott and one of us (R. G. Grainger)). In 1965 he returned as Consultant Radiologist to Chesterfield Royal Hospital where he was an admirable colleague to Dr. L. L. Ralph. John very quickly established a reputation of competence, trust and reliability which was much appreciated by all of his hospital colleagues.

John was above all a practical man, both in his work, in his leisure pursuits and in the home. He adopted a very direct approach in all of his radiological work, which gave both his patients and his colleagues advice that was always succinct, practical and reliable. He was impatient of irrelevance, humbug, fruitless speculation and unnecessary investigation. This approach permitted him to concentrate on the real issues of medicine and of life.

John had a pair of gifted hands and a practical brain that was unusually adaptable. He became a gifted silversmith creating many delightful and artistic articles. He enjoyed restoring vintage cars, working on anything mechanical and making major alterations to his house. John was a keen gardener, working many hours on his allotment, cultivating vines, brewing (and drinking) his excellent home-made beer. He would tackle anything that needed attention.

Because of his willingness to help anyone and his absolute informality and total lack of artificiality, he had very easy and open relations with everyone he met in his hospital work or socially. The radiographers took him to their hearts and he established an annual very popular tradition of addressing the Sheffield and District Radiographic Society, who accorded him honorary membership.

John had a partial gastrectomy as a medical student and was always aware of the possibility of complication. It was therefore no real surprise to him when he himself diagnosed carcinoma of the gastric remnant. During his terminal year-long illness, he and his wife Rosemary, displayed a remarkable courage. They asked only that everyone of their family and friends carry on exactly as before. Between intensive courses of chemotherapy that would have incapacitated most men, John returned to work at the hospital and was performing aortograms a few days before his death.

His funeral was attended by a very large number of friends from far and wide, reflecting the affection in which this kindly, understanding gentleman was held by all who had the privilege to know him.

His wife Rosemary and their four children showed the same braveness and practical understanding of the inevitable. The Mitchell family became a symbol of courage and faith.

All of John's colleagues and his many friends extend to Rosemary and her children our sincere sympathy, our respect and our admiration.

L. L. RALPH.
R. G. GRAINGER.

1976, *British Journal of Radiology*, *49*, 191–193 FEBRUARY 1976

Proceedings of The British Institute of Radiology

Abstracts of papers read at the Radiobiology Work-in-Progress meeting held on Friday, October 17, 1975, in the Reid-Knox Hall, Institute House, 32 Welbeck Street, London W1M 7PG*

The radiation sensitivity of *Dictyostelium discoideum*, by N. E. Gillies and N. Hariratnajothi.
Inactivation and mutation of cultured mammalian cells by radiations of different LET, by J. Thacker and R. Cox.
Problems in using neutron beams to test the theory of "oxygen production in the track", by Shirley Hornsey and T. Alper.
Monte Carlo methods for analysing the accuracy of survival-curve parameters, by N. M. Blackett and O. C. A. Scott.
Effects of radiation and hyperthermia on an *in vitro* tumour model, by R. E. Durand.
Renal function in the rat following irradiation, as monitored with a gamma-camera, by F. R. Hudson, B. M. Chauser and M. L. Law.
Tolerance of pig kidney to fractionated X-irradiation, by J. Hopewell and R. J. Berry.

THE RADIATION SENSITIVITY OF "DICTYOSTELIUM DISCOIDEUM"

By N. E. Gillies and N. Hariratnajothi

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The effect of γ rays and ultraviolet light (UV) on the viability of unaggregated cells of the slime mould *Dictyostelium discoideum* was examined. It was found that during the first 30–40 hours after the beginning of germination of the spores with bacteria on an agar surface, the cells became progressively more sensitive to γ rays. Sensitivity to UV was constant for the first ten hours after the beginning of germination, but it decreased sharply between ten hours and 20 hours, becoming constant at a new level after that time. The appearance of increased resistance to UV inactivation may represent the synthesis of an enzyme system capable of dealing with some of the UV damage, but without effect in reducing the expression of γ-ray damage. It is suggested that the increasing sensitivity to γ rays may be caused by lack of time to repair lesions during the initial period of growth after irradiation.

INACTIVATION AND MUTATION OF CULTURED MAMMALIAN CELLS BY RADIATIONS OF DIFFERENT LET

By J. Thacker and R. Cox

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Induced mutation frequencies can be measured in irradiated mammalian cell cultures by selecting cells which have acquired resistance to the cytotoxic purine analogue 6-thioguanine. These mutants are deficient in the purine salvage enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT). We have recently established for both human diploid cells and V79 Chinese hamster cells that a simple relationship exists between radiation-induced inactivation and the induction of HGPRT-deficient mutants. Despite differences in the radio-sensitivity of the two cell types, plots of induced mutation frequency *versus* log surviving fraction show the same linear relationship for both types. Radiations of low LET were used in these experiments, but preliminary data are now available for radiations with LETs in the range 50–200 keV μm^{-1}. The similarity of the mutation-survival relationships for the two cell types persists with these radiations, but the relationship may depart from linearity at low surviving fractions with radiations of LET exceeding 100 keV μm^{-1}. For both cell types, the maximum RBE for the induction of HGPRT-deficient mutants is approximately twice that found for inactivation.

PROBLEMS IN USING NEUTRON BEAMS TO TEST THE THEORY OF "OXYGEN PRODUCTION IN THE TRACK"

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If the formation of oxygen (or a similarly acting species) in the tracks of heavily ionizing particles is a valid explanation for reduction in oxygen enhancement ratios (OER) with increasing LET, it follows that measured values of K should be higher at high than at low LET (Neary, 1965). The difference in K values should equal the equivalent concentration of oxygen produced in the high LET track. Support for the oxygen-in-the-track hypothesis came from K-value measurements using *Shigella flexneri* as test organism (Alper, Moore and Bewley, 1967) and also from particle beam experiments using tests independent of the measurement of K values (Alper and Moore, 1967; Alper and Bryant, 1974). However, Howard, Gilbert and Green (1974), using the alga *Oedogonium*, and Hendry, Gilbert and Howard (1974), who made observations on colony formation by mouse bone marrow cells, failed to find that the K value "for neutrons" was greater than for X rays. Cullen (personal communication) has likewise found no difference in K values for cultured mouse ascites tumour cells with X rays and fast neutrons.

The apparent disagreement can be explained by an examination of the OERs for the different secondary charged particles produced in the neutron beam. These can be considered in two groups, the very densely ionizing α and heavy recoil particles and the less densely ionizing knock-on protons. For mammalian cells in culture Bewley, McNally and Page (1974) and Broerse, Barendsen and Van Kersen (1968) showed that the OER for the α and heavy recoils was 1. The RBE for these particles was high, so, although the α and heavy recoils gave only 20 per cent of the physical dose they were responsible for about 50 per cent of the biological damage. The OER for the neutron beam as a whole is therefore very dependent on the relative RBE values for the α plus heavy recoils and for the knock-on protons. With *Shigella* the RBE for the heavy recoil particles is probably less than 1 so they are responsible for *less* than 20 per cent of the biological effect. This explains the difference in the gain factor (OER X rays/OER neutrons) observed for entero-bacteria and mammalian cells (Alper and Moore, 1967).

Where the OER for the α's and heavy recoils is 1, the K value for the neutron beam will reflect the K value for the proton component in the dose only; a maximal estimate of the average $[O_2]$ in the track from these particles is 1 μM and this would be too small to be detected as a difference in K values for any test system for which the K value was more than about 5 μM.

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*Reprints available from the Editorial Office.

Neutron beams are therefore unsuitable sources of high LET radiation to test Neary's hypothesis, but the results which have been obtained with them are not inconsistent with the hypothesis.

REFERENCES

Alper, T., and Bryant, P., 1974. Reduction in oxygen advancement ratio with increase in LET: Tests of two hypotheses. *International Journal of Radiation Biology*, *29*, 3, 203–218.

Alper, T., and Moore, J. L., 1967. The interdependence of oxygen enhancement ratios for 250 kVp X rays and fast neutrons. *British Journal of Radiology*, *40*, 843–848.

Alper, T., Moore, J. L., and Bewley, D. K., 1967. LET as a determinant of bacterial radiosensitivity and its modification by anoxia and glycerol. *Radiation Research*, *32*, 277–293.

Bewley, D. K., McNally, N. J., and Page, B. C., 1974. Effects of secondary charged-particle spectrum on cellular response to fast neutrons. *Radiation Research*, *58*, 111–121.

Broerse, J. J., Barendsen, G. W., and Van Kersen, G. R., 1968. Survival of cultured human cells after irradiation with fast neutrons of different energies in hypoxic and oxygenated conditions. *International Journal of Radiation Biology*, *13*, 559–572.

Hendry, J. H., Gilbert, C. W., and Howard, Alma, 1975. K values and gain factors for fast neutrons and X-rays for mammalian cell cystems (CFU) *in vivo*. *Radiation Research*, *61*, 504–512.

Howard, Alma, Gilbert, C. W., and Green, D., 1974. Dependence of radiation sensitivity on oxygen tension in *Oedogonium*. III. Applicability of Howard-Flanders-Alper formula for 14 MeV neutron irradiation. *Radiation Botany*, *14*, 4, 353–356.

Neary, G. J., 1965. Chromosome observations and the theory of RBE. I. General considerations. *International Journal of Radiation Biology*, *9*, 477–502.

MONTE CARLO METHODS FOR ANALYSING THE ACCURACY OF SURVIVAL-CURVE PARAMETERS

By N. M. Blackett and O. C. A. Scott

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A means for investigating the accuracy of estimates of radiobiological parameters is described, which makes use of a computer to generate hypothetical survival-curve data (using random numbers) based on defined values of D_0 and N. This data can be used to obtain estimates of D_0 and N by whatever method of curve fitting is desired. Repetition of this process many times gives the mean estimated value and its standard deviation. Different sources of experimental variation can be introduced that may conform to different distributions thus allowing one to depart from standard statistical assumptions such as normally distributed errors and independence of individual measurements.

The possibility of introducing bias into the estimates of radiobiological parameters and the size of the standard error can be compared for different curve fitting procedures for circumstances closely resembling those obtained in practice. Application of this method to the Pike-Alper program for determining dose modifying factors confirms that a considerable improvement in the accuracy of the estimate of the D_0 ratio is obtained provided the N values for the two curves are the same.

However if the N values are not the same the method introduces a systematic bias into the estimate of the D_0 ratio so that the true ratio can be outside the 95 per cent confidence limits given by the program. This demonstrates the need for external evidence that the two N values are the same before the program can be used correctly.

The method described can be applied to a wide variety of problems without requiring a detailed mathematical knowledge of statistics.

EFFECTS OF RADIATION AND HYPERTHERMIA ON AN "IN VITRO" TUMOUR MODEL

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Hyperthermia has recently received attention as a potential anti-cancer agent, due in part to preliminary observations that hypoxic cells may be more thermosensitive than well-oxygenated cells. Histological observations of heat-treated multicell "spheroids", in *in vitro* tumour models which display central hypoxia and necrosis similar to that observed in many nodular tumours *in vivo*, tend to support this suggestion. However, quantitative hyperthermic studies of the viability of individual cells from the hypoxic and well-oxygenated regions of spheroids have not proved as optimistic.

The thermo-resistance of cells grown as small spheroids is increased above that of single cells, analogous to the enhanced radioresistance previously observed under these growth conditions. A further increase in thermo-resistance has been noted for larger spheroids, apparently due to the accumulation of non-cycling, heat-resistant cells. In still larger spheroids, the development of hypoxic cells does not, however, lead to appreciable thermal sensitivity. Thus, the hyperthermic killing of spheroid cells is qualitatively similar to killing by radiation.

Heat can, however, be effectively used as an adjuvant to radiation. The synergistic interaction between the modalities is well known, but a further potentiation has been observed in the spheroid system. The latter effect is apparently due to changes in metabolic activity of heated cells—that is, the respiration (oxygen consumption) of cells is inhibited at temperatures greater than 42°C, leading to greater penetration of oxygen into the spheroid with a concomitant increase in net cellular radiosensitivity. Thus, hyperthermia indirectly potentiates the response of the *previously* hypoxic cells. This may account, at least in part, for the apparent enhancement of hypoxic-cell-killing by combined treatment with heat and radiation.

RENAL FUNCTION IN THE RAT FOLLOWING IRRADIATION AS MONITORED WITH A GAMMA-CAMERA

By F. R. Hudson, B. M. Chauser and M. P. Law

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Effective renal plasma flow (ERPF) in the rat was measured by monitoring the uptake and clearance of ^{123}I-hippuran, using a gamma-camera coupled to a computer for data processing. A pinhole collimator was employed to give clearly-defined images which were used to estimate plasma flow to each kidney. Normal values of total ERPF in the rat were found to be 2·9 ml./minute/100 g body weight. The technique has been used to monitor the effects of single doses of 1,000, 2,000, and 3,000 rads 250 kVp X rays on a single kidney. Major renal failure was observed 18 weeks after 2,000 rads and slightly earlier after 3,000 rads. Renal failure may be related with the development of fibrosis and collagen deposition. The collagen content of each kidney was measured by estimating hydroxyproline, an amino acid which is specific to collagen. It was increased in irradiated kidneys 20 weeks after doses of 2,000 and 3,000 rads. There was a positive correlation between collagen content and loss of kidney function. This was independent of dose suggesting that they may be causally related.

TOLERANCE OF PIG KIDNEY TO FRACTIONATED X-IRRADIATION

By J. W. Hopewell and R. J. Berry

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The effects of X-irradiation on the kidney of the Large White pig has been used as a model for determining time and fractionation factors for predicting renal tolerance. In each animal one kidney was irradiated with one of six fractionation régimes; single doses, 6 or 14 fractions in 18 days and 6, 14 or 30 fractions in 39 days. Renal tolerance was determined by the presence or absence of significant function in the irradiated kidney, as compared with the contralateral unirradiated kidney in the same animal, using ^{131}I Hippuran renography.

The levels of renal tolerances obtained six months after treatment with the fractionated doses are confirmed by subsequent renograms carried out for periods up to two years after treatment. For kidneys treated daily (14F/18 days or 30F/39 days) with total doses 15 to 30 per cent below tolerance, however, a transient loss of function was observed 18 months after treatment. Function had returned in these animals at two years.

Kidney weights obtained when animals were killed supported the levels of tolerance obtained by functional studies. Kidneys with no function weighed less than 30 g while those showing evidence of function had weights in excess of 80 g.

The tolerance levels obtained showed that renal tolerance could not be predicted by a simple mathematical formula. The fractions exponent was found to vary with the overall treatment time (0·24 for 6 and 14 fractions in 18 days and 0·49 for 6, 14 and 30 fractions in 39 days) as did the time exponent for a fixed number of fractions (0·11 for 6 fractions given between 18 and 39 days and 0·38 for 14 fractions given over the same time period).

The levels of renal tolerance determined in the pig correlated well with accepted levels of tolerance used in clinical practice.

Book reviews

MRC Report 1975: Criteria for controlling radiation doses to the public after accidental escape of radioactive material, pp. vii+48, 1975 (H.M.S.O.), £1·30.

Previous MRC Reports (1959–61) have also dealt with this topic, but new metabolic and dosimetric data made available over the past 14 years have enabled revised and more comprehensive calculations to be made of the levels of radiation dose that warrant remedial action in the event of the accidental escape of radioactive materials into the environment. While the ICRP have recommended criteria for regulating "controllable" exposures, it is appropriate that the MRC should provide criteria for "uncontrolled sources" since these would specifically refer to social conditions in the United Kingdom.

The Council have revised their emergency reference levels of dose (ERLs) for various body tissues and the data used and methods of calculation are given in the appendices of the report. The report also discusses the release of radionuclides that could occur when an operating reactor is involved in an accident and concludes that in addition to ^{89}Sr, ^{90}Sr, isotopes of iodine, ^{132}Te and ^{137}Cs, other nuclides such as ^{242}Cm, ^{95}Zr, ^{106}Ru, ^{140}Ba, and ^{144}Ce might also be of importance as far as internal radiation doses are concerned.

The intention of the report is to give guidance to all who are concerned with plans for the public in the event of a release of radioactive material. It recommends that there should be a "single standing body" namely the National Radiological Protection Board to advise on the interpretation and application of the general principles discussed in the report.

The report deals in detail with ERLs for isotopes of iodine, ^{137}Cs, ^{89}Sr and ^{90}Sr in air and milk and pasture and those for insoluble particles in lung. Although as stated the report is intended for those who might be engaged in taking counter-measures to reduce the radiation exposure to individuals or populations it will also be of scientific interest to all who are engaged in radiation protection. In addition it contains useful dosimetric data.

T. H. E. Bryant.

Radiology in Primary Care. 17 authors, Edited by Glenn V. Dalrymple and John E. Slayden, pp. 330, 1975 (Saint Louis, The C.V. Mosby Co., distributed in Britain by Henry Kimpton), £11·25.

This book is directed toward the primary physician in training and practice, says the Preface. You might innocently suppose that it would therefore aim at teaching clinicians how to make best use of their X-ray departments and radiologists. In fact, this book is for those in medical practice who want to set up their own X-ray suite alongside their consulting-room, with hardly a radiologist in sight.

The volume is concise and remarkably comprehensive, taking in the basic physics of X-ray production and absorption, design of the X-ray room, equipment, radiation protection and biology. The bulk of the book describes and illustrates the basic radiographic projections, including exposure factors, with simple examples of abnormal radiographs. As it is meant for general practice, its longest chapter is rightly that on orthopaedics. Intravenous urograms and cholecystograms are discussed in detail, but the do-it-yourself approach stops short of special examinations like barium meals.

The immediate reaction of radiologist readers could be unprintable, because this is of course heresy, poaching, putting the clock back, etc. Indeed, the pitfalls of amateur radiological practice are lit up by the book's plea that the doctor should engage a qualified radiographer, rather than train his own staff. The implication is that someone unqualified might commonly do the radiography in this setting.

At first sight the possible appeal of this book in Britain appears rather limited—it is not for the radiologist in training. But whether radiologists can or should cope with the whole burden of X-ray services is now under discussion here (see "Must radiologists do all the reporting", *B.J.R.*, July, 1975, p. 517). If general practitioners interested in radiology come to look after an X-ray room in the small community hospital, this book would make a very good primer for them.

T. Sherwood.

1976, *British Journal of Radiology*, *49*, 194

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

UPTAKE OF PERTECHNETATE IN MAMMARY TISSUE

In a recent case report Carmody and Highman (1975) described unusual activity in the mammary tissue of a patient who underwent a lung scan two days after delivery. It was calculated that the patient had received 225 μCi of free pertechnetate.

The authors stated that they could find no references to pertechnetate concentrations in active mammary tissue, and they commented that they were unable to obtain a sample of breast milk to ascertain any possible hazard to the infant.

Although not relating to mammary tissue as such but rather to the milk content thereof, I would like to draw your attention to a case report (Wyburn, 1974) in which was described the milk excretion levels of four nursing mothers who had received technetium compounds. Substantial levels of ^{99}Tc^{m} were demonstrated in the milk, one case receiving 12 mCi of ^{99}Tc^{m} pertechnetate having a level of 0·61 μCi/ml. two hours after injection. Other authors (Vagenakis, Abreau and Braverman, 1971) reporting on a single case receiving 10 μCi of pertechnetate, described levels which at one stage, 22 hours after injection, were 44 times the level found in one of my reported cases receiving a similar activity. No earlier samples were, however, taken in this case.

Taking into account the large range in thyroid uptake of pertechnetate in the infant and the range in milk consumption, an acceptable level for commencing breast feeding was postulated as one-tenth of the maximum level for continuous exposure as recommended by the ICRP, *i.e.* 6×10^{-3} μCi/ml. In a case receiving 225 μCi of pertechnetate it seems probable from my data that this level would have occurred in the milk from 4 to 12 hours after injection. It is important to note, however, that the maximum milk activity levels reported to date from pertechnetate injections would seem insufficient to account for an activity in the breast which would show up on a scintigram if an activity of only 225 μCi were given. Possibly the range of excretion levels is even greater than previously reported or there is a high tissue/milk ratio.

Yours, etc.,
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REFERENCES

CARMODY, R., and HIGHMAN, J. H., 1975. Uptake of pertechnetate in mammary tissue and thyroid after pregnancy. *British Journal of Radiology*, *48*, 63–64.

VAGENAKIS, A. G., ABREAU, C. M., BRAVERMAN, L. E., 1971. Duration of radioactivity in the milk of a nursing mother following ^{99m}Tc administration. *Journal of Nuclear Medicine*, *12*, 188.

WYBURN, J. R., 1974. Human breast milk excretion of radionuclides following administration of radiopharmaceuticals. *Journal of Nuclear Medicine*, *2*, 115–117.

THE EDITOR—SIR,

MEASUREMENT OF PNEUMOCONIOSIS IN CHEST RADIOGRAPHS BY COMPUTER

In epidemiological studies it is sometimes necessary to assess the severity of pneumoconiosis in each of several thousand chest radiographs. In each case the radiological question to be answered is not "Is this chest film abnormal?" but "How severe is the pneumoconiosis evident in this chest film?" where *severity* is to be measured on the 12-point scale adopted as the basis of an internationally agreed set of rules for the "measurement" of pneumoconiosis in chest films (ILO, 1970). Since so many films are involved and the question to be answered is so comparatively well defined, we may reasonably ask whether the assessment can be made by a suitably programmed computer.

We describe the performance of a computer program for measuring pneumoconiosis in chest films. The 93 films used in this study are chest radiographs of coal-miners in the Rhondda, and have been chosen to include a high proportion of the smallest (p-type) opacities. Each film has been independently read by Dr. J. C. Gilson and Dr. A. L. Cochrane who are acknowledged experts in this field. No attempt was made to select only films of good radiographic quality.

Two computer programs (Jagoe and Paton, 1975; 1976), were applied to each film, first to decide which areas should be considered (by the computer) as the lung fields and second to define a value which we call the *computed score* for each film.

In order to compare the computed score with the score assigned by the human observer it is necessary to replace the ILO 12 point scale of (0/–, 0/0, 0/1, 1/0, 1/1, 1/2, 2/1, 2/2, 2/3, 3/2, 3/3, 3/4) by a numerical one. We follow Rossiter (1972) in using the values (−1·44, −0·22, 0·72, 1·12, 1·43, 1·78, 2·04, 2·50, 3·04, 3·42, 4·24, 5·36). Thus an ILO score of 0/– is equivalent to one of −1·44 Rossiter units.

Figure 1 shows the distribution of computed score and Dr. Gilson's score for the 93 films. The correlation is 0·64. This value is to be interpreted in the light of Fig. 2 which shows the distribution of Gilson-scores and Cockrane score for the same 93 films. The correlation between the scores assigned by these two highly skilled human observers is 0·72.

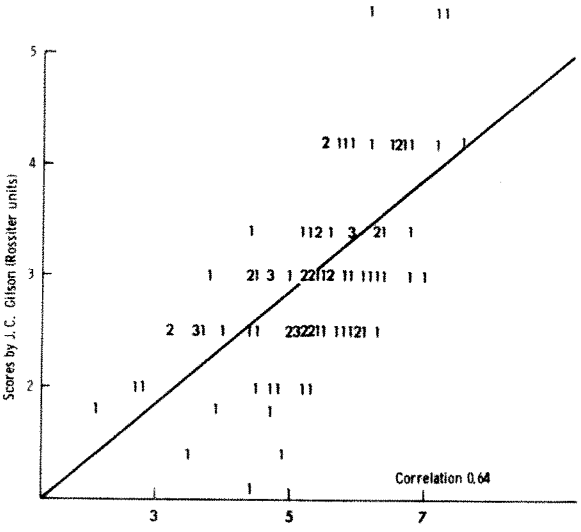

FIG. 1.

1976, *British Journal of Radiology*, *49*, 195–196 FEBRUARY 1976

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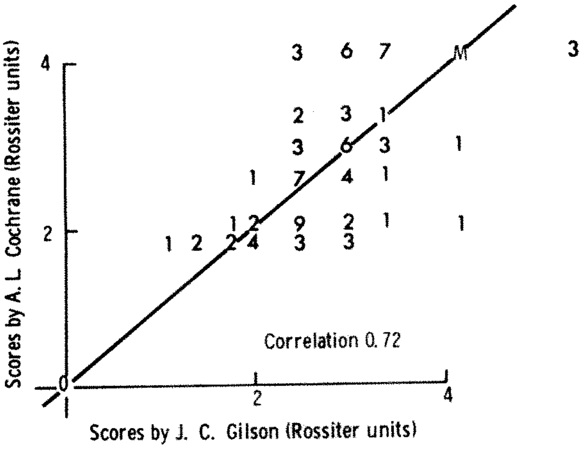

FIG. 2.

If the 93 films used in this study are typical of those encountered in epidemiological work then the computer programs we have developed may form the basis of an automatic method of measuring pneumoconiosis for use in epidemiological work.

Yours, etc.,
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REFERENCES

ILO, 1970. *International Classification of Radiographs of Pneumoconioses (Revised 1968), Occupational Safety and Health Series No. 22* (Geneva, International Labour Office).

JAGOE, J. R., and PATON, K. A., 1975. Reading chest X-rays for pneumoconiosis by computer. *British Journal of Industrial Medicine*, *32*, 267–272.

1976. Measurement of pneumoconiosis by computer. *Institute of Electrical and Electronic Engineers Transactions on Computers* (to appear January 1976).

ROSSITER, C. E., 1972. Relation between content and composition of coal workers' lungs and radiological appearances. *British Journal of Industrial Medicine*, *29*, 31–44.

THE EDITOR—SIR,

RE-EVALUATION OF PUBLISHED NEUTRON RBE VALUES FOR MOUSE INTESTINE

The intestinal microcolony assay technique (Withers and Elkind, 1970) which measures the survival of mouse intestinal crypts, has been used by several authors (detailed below) to determine neutron RBE values at different centres. The values have shown a marked variation. Recent informal neutron dosimetry intercomparisons between centres has enabled the RBE values to be compared with reference to a common dose standard.

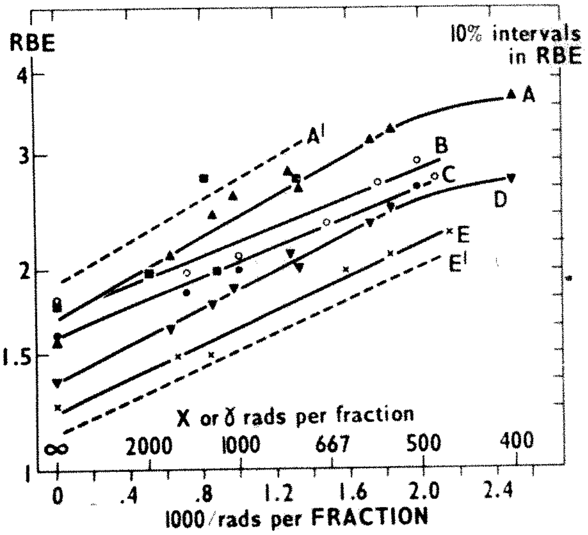

FIG. 1.

RBE (log) versus 1,000/X or γ-ray dose per fraction. Intervals of 10 per cent in RBE shown on right ordinate. Doses referred to arbitrary standard of Manchester/Tamvec dosimetry.

Curve A and solid squares—Hammersmith, 16 MeV D on Be (Hornsey, 1973).
Curve A and solid triangles—Tamvec, 16 MeV D on Be (Withers *et al.*, 1974).
Curve B and open circles—Manchester, collimated 14 MeV D-T (Hendry *et al.*, 1975).
Curve C and solid circles—repeat of B at 10 cm depth (Hendry *et al.*, 1975).
Curve D and solid inverted triangles—Tamvec, 50 MeV D on Be (Withers *et al.*, 1974).
Curve E and crosses—Rijswijk, uncollimated D-T (Broerse *et al.*, 1971; Broerse and Roelse, 1971).
Curves A and E′—curves A and E respectively, before doses modified to common dose standard.

Neutron sources are referred to by site name, *i.e.* D-T neutrons at Manchester and Rijswijk, and Cyclotron-produced neutrons at Hammersmith and Houston (Tamvec). Neutron dose-rate has an extreme range of 10 to 100 rad/min in the experiments. Dosage intercomparisons have been performed between Manchester and Rijswijk, Hammersmith and Manchester, and Tamvec and Hammersmith. An arbitrary reference standard of Manchester/Tamvec is adopted here, as quoted doses at these two centres differ by only 1 per cent. On these considerations, published neutron doses have been multiplied by factors of 1·0 (Manchester), 0·99 (Tamvec), 1·11 (Hammersmith) and 0·93 (Rijswijk). The resultant RBE comparisons are shown graphically in Fig. 1, on a (modified) plot described by Alper (1972). A horizontal line on such a plot would represent the RBE as a constant dose-modification factor, irrespective of the fractionation régime. Log RBE is used for the ordinate, so that dose-modification is demonstrated by a vertical shift in a line (*i.e.* parallel lines). The dose per fraction of the reference radiation is shown on the abscissa, as apart from the evidence of Broerse (1969), the response of this tissue to 300 kV rays (30 or 650 rad/min) or ^{137}Cs γ rays (540 rad/min) (Hendry, Major and Greene, 1975), and 250 kV X rays or 7 MeV X rays (200 rad/min (Hornsey and Silvester, 1974) is found to be similar. In general, RBE is a function of dose, and at high doses it approaches a limiting value which is given by the D_0 ratio. This value corresponds to zero on the lower abscissa in Fig. 1. For single and fractionated doses, the RBE values have been read from the top and bottom of published curves, where data have been presented between about 80 per cent and about 1 per cent crypt survival.

The data in Fig. 1 show the marked change in RBE with dose per fraction for this tissue, and the difference in response to various neutron beams. The original published RBE values (curves A′ and E′) show a more marked divergence than is present when the physical dose measurements are referred to a common standard. The RBE values for neutrons generated by 16 MeV D on Be at two independent centres (Hammersmith and Tamvec) are brought into agreement, and the values for neutrons generated by 50 MeV D on Be are intermediate between those for collimated and uncollimated 14 MeV D-T neutrons. (It is of interest that the results of Withers, Brennan and Elkind (1970) for uncollimated 14 MeV D-T neutrons fall precisely on the curve E′.) The slopes of the lines in Fig. 1 for cyclotron neutrons are in general higher than those for D-T neutrons, indicating an expected greater "shoulder reduction" with these beams.

At 500 rad X rays per fraction—the lowest dose where RBE comparisons are still possible—estimated RBE values are 3·40 (curve A), 2·85 (B), 2·65 (C), 2·55 (D), and 2·20 (E). It should be remembered that (a) dosimetric errors on the RBE differences are ±2–3 per cent, but about ±8 per cent in absolute values, (b) RBE differences for radiotherapeutic dose fractions of 200–300 rad X rays may be marginally greater than those at 500 rad.

The intestinal microcolony assay is one biological system that could be used as a "biological dosimeter" for radiations of different LET (*e.g.* Berry, 1974). However, the universality of such comparisons is uncertain, as there is some disagreement as to whether RBE values for this tissue are similar to those for other tissues (*e.g.* van der Kogel and Barendsen, 1974) or slightly higher, *e.g.* 20 per cent higher than for skin (Field and Hornsey, 1971).

Yours, etc.,
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REFERENCES

ALPER, T., 1972. Aspects of neutron therapy based on an analysis of relationships between RBE and dose. *British Journal of Radiology*, *45*, 39–47.

BERRY, R. J., 1974. In *Proceedings of biological effects of neutron irradiation*, p. 257 (I.A.E.A. Vienna).

BROERSE, J. J., 1969. Dose-mortality studies for mice irradiated with X-rays, γ-rays and 15 MeV neutrons. *International Journal of Radiation Biology*, *15*, 115–124.

BROERSE, J. J., BARENDSEN, G. W., FRERIKS, G., and VAN PUTTEN, L. M., 1971. RBE values of 15 MeV neutrons for effects on normal tissues. *European Journal of Cancer*, *7*, 171–177.

BROERSE, J. J., and ROELSE, H., 1971. Survival of intestinal crypt cells after fractionated exposure to X-rays and 15 MeV neutrons. *International Journal of Radiation Biology*, *20*, 391–395.

FIELD, S. B., and HORNSEY, S., 1971. RBE values for Cyclotron neutrons for effects on normal tissues and tumours as a function of dose and dose fractionation. *European Journal of Cancer*, *7*, 161–164.

HENDRY, J. H., MAJOR, D., and GREENE, D., 1975. Daily D-T neutron irradiation of mouse intestine. *Radiation Research*, *63* 149–156.

HORNSEY, S., 1973. The effectiveness of fast neutrons compared with low LET radiation on cell survival measured in the mouse jejunum. *Radiation Research*, *55*, 58–68.

HORNSEY, S., and SILVESTER, A., 1974. The relative effectiveness of super- and orthovoltage X rays for intestinal damage in man and mouse: an apparent discrepancy and its explanation. *British Journal of Radiology*, *47*, 670–672.

VAN DER KOGEL, A. J., and BARENDSEN, G. W., 1974. Late effects of spinal cord irradiation with 300 kV X-rays and 15 MeV neutrons. *British Journal of Radiology*, *47*, 393–398.

WITHERS, H. R., and ELKIND, M. M., 1970. Microcolony survival assay for cells of mouse intestinal mucosa exposed to radiation. *International Journal of Radiation Biology*, *17*, 261–267.

WITHERS, H. R., BRENNAN, J. T., and ELKIND, M. M., 1970. The response of stem cells of intestinal mucosa to irradiation with 14 MeV neutrons. *British Journal of Radiology*, *43*, 796–801.

WITHERS, H. R., MASON, K., REID, B. O., DUBRAVSKY, N., BARKLEY, H. T., BROWN, B. W., and SMATHERS, J. B., 1974. Response of mouse intestine to neutrons and gamma-rays in relation to dose fractionation and division cycle. *Cancer*, *34*, 39–47.

THE EDITOR—SIR,

ABSORBED DOSE TO THE BLADDER FROM ^{99}Tc^{m} DTPA

In the course of renal scanning using ^{99}Tc^{m} DTPA, it became apparent that the generally quoted dosimetry, with an absorbed dose to the bladder of 555 mrad. mCi^{-1} (Hauser, Atkins and Nelson, 1970), was incompatible with the accepted routine use of 10–15 mCi or 200 μCi.kg^{-1} of ^{99}Tc^{m} DTPA (Atkins *et al.*, 1973; Handmaker, McRae and Buck, 1973; Kilburn, Howlett and Gilday, 1973). However, the value quoted above was determined on the assumption that the activity all remained in the body, *i.e.* the patient does not pass urine. A more realistic value for bladder dose can be obtained if the patient is assumed to form and pass urine.

The absorbed dose to the bladder from radionuclides in urine has been studied by Unnikrishnan (1974), with particular reference to ^{131}I-Hippuran. He assumed either that the whole activity enters the bladder at zero time or the activity enters the bladder at a constant rate, and that once micturition is achieved, no more activity enters the bladder. Unnikrishnan points out that the MIRD pamphlet No. 5 (Snyder, *et al.*, 1969) gives the absorbed fractions for a static bladder plus contents whereas in reality the bladder wall is the target region (Cottrall, Taylor and Unnikrishnan, 1971). Consequently he determined the absorbed dose resulting from photon irradiation by employing the results of Snyder, Ford and Warner, (1970), who have evaluated the dose rate at the bladder wall from monoenergetic gamma emitters for seven specific volumes of contents ranging from 0 to 500 ml. Since the volume of the bladder is continuously changing, application of this method in the present case requires careful interpolation. In view of this, it is more straightforward to employ a direct analytical method of calculation.

In the model presented here the ^{99}Tc^{m} DTPA is assumed to be cleared in a single exponential manner to a spherical bladder by glomerular filtration. The flow rate of urine into the bladder is constant. The volume of the bladder increases linearly with time until some elapsed time T when the bladder empties instantaneously and its volume returns to zero. The cycle of re-filling and emptying continues indefinitely with a period of T. The period T is referred to in the text as the bladder emptying period.

The decay system for ^{99}Tc^{m} is presented in Table I. For the purpose of the present calculations, the average energy ($\bar{E}$) released in each internal conversion is taken to be 0·125 MeV. This comprises the kinetic energy of the conversion electrons plus the energy of the Auger electrons weighted by the fluorescence yield for ^{99}Tc^{m}.

TABLE I

DECAY SCHEME OF ^{99}Tc^{m}

Type of decay—Isomeric transition Transition probability—100%		
Photon energy MeV	Photons emitted, %	Transitions internally converted, %
0·002	~0	99·1
0·141	88·5	10·6
0·143	0·03	0·87

(Martin and Blichert-Toft, 1970)

The exposure rate due to the photon radiation at some time t on the surface of a sphere of radius $r(t)$ cm, including absorption and scattering of radiation within the sphere, may be shown to be (Morgan and Emerson, 1967).

$$X(t)=\Gamma S(t)\,\frac{2\pi}{\mu}\left[1-\frac{1-e^{-2\mu r(t)}}{2\mu r(t)}\right] \quad . \quad . \ (1)$$

where Γ is the exposure rate constant for ^{99}Tc^{m} ($\Gamma=0{\cdot}72$ Rcm^{2}h^{-1}mCi^{-1}; McAfee and Subramanian, 1969), and μ is the energy absorption coefficient in water at 141 keV ($\mu=0{\cdot}027$ cm^{-1}; ICRU, 1970).

$S(t)$ is the activity of ^{99}Tc^{m} per unit volume in the sphere at time t, given by

$$S(t)=\frac{A}{Ft}(1-e^{-\lambda_1 t})e^{-\lambda_2 t} \quad . \quad . \quad . \ (2)$$

where A is the injected activity of ^{99}Tc^{m} (mCi),
λ_1 is the decay constant of blood clearance (h^{-1}),
λ_2 is the physical decay constant of ^{99}Tc^{m} (h^{-1}),
F is the flow rate of urine into the bladder (ml.h^{-1}).

The radius $r(t)$ is given by

$$r(t)=\left[\frac{3\,F\,t}{4\pi}\right]^{\frac{1}{3}} \quad . \quad . \quad . \ (3)$$

The absorbed dose on the surface of the sphere in the first period T resulting from gamma irradiation is

$$Dg=\frac{2\pi\Gamma f A}{\mu F}\int_0^T(1-e^{-\lambda_1 t})\,e^{-\lambda_2 t}\,\frac{1}{t}\left[1-\frac{1-e^{-2\mu r(t)}}{2\mu\, r(t)}\right]dt \text{ rad} \quad (4)$$

where f is the Röntgen to rad conversion factor for soft tissue at 141 keV ($f=0{\cdot}96$).

If $r(t)$ is much greater than the maximum range of the conversion electrons, the absorbed dose rate (rad.h^{-1}) resulting from conversion and Auger electrons at time t on the surface of the sphere is

$$\mathcal{J}(t)=1065{\cdot}6\ n\ S(t)\ \bar{E} \quad . \quad . \quad . \quad . \quad . \quad . \ (5)$$

(Young, 1967)

where n is the number of electrons of energy $\bar{E}$ (MeV) emitted per disintegration.

The absorbed dose on the surface of the sphere in the first period T resulting from electron irradiation is

$$De=1065{\cdot}6\,n\,\bar{E}\frac{A}{F}\int_0^T(1-e^{-\lambda_1 t})e^{-\lambda_2 t}\frac{1}{t}\,dt \text{ rad} \quad . \ (6)$$

Equations (4) and (5) are evaluated numerically using Simpson's rule of numerical integration. Since the bladder is continuously re-filling and emptying, the total absorbed dose to the internal bladder wall will be

$$D_T=(Dg+)De\sum_{m=0}^{\infty}\exp\left((-\lambda_1-\lambda_2)\,m\,T\right)\text{ rad} \quad . \ (7)$$

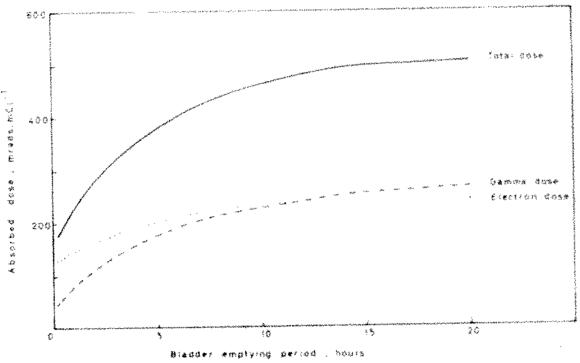

FIG. 1.

Electron dose, γ–ray dose and total absorbed dose to the internal bladder wall as a function of bladder emptying period.
Injected activity, 1 mCi
Urine production rate, 90 ml.h^{-1}
Blood half-clearance time, 1·5 h.

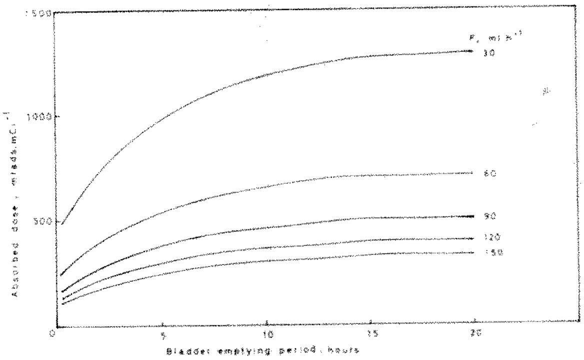

FIG. 2.

Variation of total absorbed dose with bladder emptying period for different urine production rates (F).
Injected activity, 1 mCi
Blood half-clearance time, 1·5 h.

The total absorbed dose (D_T), together with the contributions from the photon and electron radiations, are plotted as a function of bladder emptying period (T) in Fig. 1 for an injected activity of 1 mCi (A), a typical urine production rate (F) of 90 ml.h^{-1} and a blood half-clearance time of 1·5 hours (corresponding approximately to a glomerular filtration rate of 120 ml.min^{-1}). The maximum range in soft tissue of the conversion electrons is 0·02 cm and consequently at depths in the bladder wall greater than this, only the photon radiation will contribute to the absorbed dose.

Figure 2 shows the variation of total dose per mCi with bladder emptying period for different urine production rates.

It can be seen that it is important that the patient should be well hydrated and encouraged to pass urine frequently after the examination. Provided these precautions are observed, the bladder dose is kept well within acceptable limits.

We should like to thank Mr. J. R. Corfield for his helpful comments on this work.

Yours, etc.,
B. L. Diffey

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A. J. W. Hilson

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REFERENCES

Atkins, H. L., Klopper, J. F., Eckelman, W. C., and Richards, P., 1973. The Technetium-99m DTPA renal study. In *Medical Radioisotope Scintigraphy Vol. II*, pp. 251–261 (I.A.E.A., Vienna).

Cottrall, M. F., Taylor, D. N., and Unnikrishnan, K., 1971, Absorbed dose calculations. *Journal of Nuclear Medicine*, *12*, 841–842.

Handmaker, H., McRae, J., and Buck, E. G., 1973. Intravenous radionuclide voiding cystography, *Radiology*, *108*, 703–705.

Hauser, W., Atkins, H. L., and Nelson, K. G., 1970. ^{99}Tc^{m} DTPA: A new radiopharmaceutical for brain and kidney scanning, *Radiology*, *94*, 679–684.

ICRU Report, 17, 1970. Radiation Dosimetry: X rays generated at potentials of 5–150 kV.

Kilburn, E., Howlett, L., and Gilday, D. L., 1973. Renal studies in children using ^{99}Tc^{m}, DTPA. *Journal of Nuclear Medicine*, *14*, 473–474.

Martin, M. J. and Blichert-Toft, P. H., 1970. Radioactive atoms: Auger electrons, α–β–γ and X-ray data. *Nuclear Data Tables A8*, 74–76 (Academic Press, New York).

McAfee, J. G. and Subramanian, G., 1969. Appendix tables on radiopharmaceuticals. In *Clinical Scintillation Scanning*, Eds. L. M. Freeman and P. M. Johnson, pp. 533 (Hoeber, New York).

Morgan, K. Z., and Emerson, L. C., 1967. Dose from external sources of radiation. In *Principles of Radiation Protection*, Eds. K. Z. Morgan and J. E. Turner, pp. 285 (John Wiley & Sons Inc., New York).

Snyder, W. S., Ford, M. R., Warner, G. G., and Fisher, H. L., 1969. Estimates of absorbed fractions for monoenergetic photon sources uniformly distributed in various organs of a heterogeneous phantom. MIRD pamphlet No. 5. *Journal of Nuclear Medicine Supplement*, 3, 7–52.

Snyder, W. S., Ford, M. R., and Warner, G. G., 1970. *Health Physics Division Annual Report*, ORNL–4584 (USAEC, Oak Ridge National Laboratory, Tennessee).

Unnikrishnan, K., 1974. Dose to the urinary bladder from radionuclides in urine, *Physics in Medicine and Biology*, *19*, 329–340.

Young, M. E. J., 1967. *Radiological Physics*, Second Edition, p. 493 (H. K. Lewis & Co. Ltd., London).

The Editor—Sir,

Comparative Effectiveness of Radiotherapy Treatment Schemes

The recent publication of a letter in your Journal (Ellis, 1974) discussing the comparative effectiveness of a variety of radiotherapy treatment schemes has prompted me to question the validity of the application of the "Target Theory", which appears to be universally accepted, to the interpretation of cell survival data.

"Best fits" can always be obtained for any collection of data, but for graphs exhibiting high extrapolation numbers, best fits are invariably poor fits at low dosage. If, for example, the single-hit multi-target expression used by Ellis were to be applied to a single exposure of 200 rads under the conditions quoted from Dewey (1971), a survival of 92 per cent would be expected, whereas a figure near to 50 per cent is given in the original paper. It should be noted that formulae of this type are strictly only true at the values of d_0 and N from which they were derived. They may not, in general, be taken as equations to the curve containing these points and may well be grossly inaccurate when applied at threshold (*e.g.* treatment) levels if d_0 and the extrapolation number have been derived from the "straight line" portion of the survival curve.

For practical purposes, many of the published survival curves can be very closely represented by an empirical law of the form

$$S = e^{-mx^{p}} \quad . \quad . \quad . \quad . \quad (1)$$

It is found, for example, that the published curve due to Dewey, referred to above, can be very closely matched by putting $m = 8{\cdot}00$ and $p = 1{\cdot}52$ when the dose, x, is given in kilorads.

Similarly, the survival curve for well-oxygenated cells irradiated with ^{60}Co radiation, due to Wilson (1961) and used later by Stewart (1968) to illustrate the functional basis of his calculator for fractionated doses, may be more closely fitted by a curve of the same form in which $m = 5{\cdot}49$ and $p = 1{\cdot}48$. The corresponding curve for anoxic cells, given by Wilson in the same paper, may be fitted by putting $m = 1{\cdot}66$ and $p = 1{\cdot}36$.

Fowler and Stern (1963) had proposed that cell survival might be better represented by raising the exponent to quadratic form, and they, among others, have illustrated a simple power relationship between the total dose given in several fractions and the number of daily fractions, *i.e.* $\log \dfrac{nx_n}{x_1} = k \log n$. If it may be inferred that the time-dependence contained within this expression may be equated with that contained within the multiple application of equation (1), then $x_1{}^{p} = nx_n{}^{p}$ and $\dfrac{1}{p} = 1 - k$.

When applied to the N.S.D. concept of dosage equivalence, that is; $nx_n = x_1\, n^{0\cdot24}\, t^{0\cdot11}$, one finds that $-\log S = mx_1{}^{p} = m\,(n^{0\cdot76}\, t^{-0\cdot11}\, x_n)^{p} = m\, \left(\dfrac{n}{t}\right)^{0\cdot11p} nx_n{}^{p}$ when $p = 1{\cdot}538$, so that $-\log S = mnx_n{}^{p}$ when $n = t$ also.

It should be noted, however, that curves of similar shape can be produced from consideration of competitive mass-action repolymerization within the cell following irradiation but before restitution of proliferation. Similar mathematical considerations have been made by Sacher and Trucco (1966) to the regeneration of cell populations after irradiation, but applied to the division of intact cells.

If it is assumed that the instantaneous apparent survival following short-duration exposure is entirely exponential (*i.e.* $S_0 = e^{-\alpha x}$), then recovery will proceed to the observed value

$$S_t = S\infty \left\{ 1 + \left(\frac{S\infty}{S_0} - 1 \right) q \right\}^{-1} \quad . \quad . \quad (2)$$

where $S\infty = e^{-\beta x}$ is an upper bound to potential recovery. q is a monotone decreasing function of time which could take the form $\exp\left\{ -\gamma\,(1 - e^{-\mu t}) \right\}$ or say $\left(\dfrac{t}{t_0}\right)^{-\gamma}$ depending upon the differential equation that is chosen to characterize the process of recombination. At high dosage, N tends to q^{-1} and d_0 tends to α^{-1}.

An illustration of this may be obtained by reference to Winans, Dewey and Dettor (1972), in which the data reproduced in their Fig. 5, describing cellular repair processes at 37°C and 20°C, can be closely matched by putting a, β and q equal to 12·8, 3·13 and 0·004 and 12·1, 2·79 and 0·003 respectively.

I am not able to offer any unique mathematical connection between formulas (1) and (2) but suggest that they may be useful separately as follows:

Equation (1), or its NSD counterpart involving time, might be employed to advantage in practical radiotherapy to calculate comparative cell survival distributions throughout a course of treatment.

The mechanism of cellular damage and repair is better represented by the second expression in which the effects of anoxia and other protective agents are related to a low value of β whilst, conversely, a high value of β would be expected as a result of high density LET or the presence of chemical agents which inhibit repolymerization.

Yours, etc.,
J. P. HUGGETT.

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Tunbridge Wells, Kent TN4 0NL.

REFERENCES

DEWEY, D. L., 1971. The radiosensitivity of melanoma cells in culture. *British Journal of Radiology*, *44*, 816–817.

ELLIS, F., 1974. The NSD concept and radioresistant tumours. *British Journal of Radiology*, *47*, 909.

FOWLER, J. F. and STERN, B. E., 1963. Dose-time relationships in radiotherapy and the validity of cell survival curve models. *British Journal of Radiology*, *36*, 163–173.

ORTON, C. G., and ELLIS, F., 1973. A simplification in the use of the NSD concept in practical radiotherapy. *British Journal of Radiology*, *46*, 529–537.

SACHER, G. A., and TRUCCO, E., 1966. Theory of radiation injury and recovery in self-renewing cell populations. *Radiation Research*, *29*, 236–256.

STEWART, F. S., 1968. A calculator for fractionated doses. *British Journal of Radiology*, *41*, 792–794.

WILSON, C. W., 1961. Possible implications of recent observations for tumour-dose-fractionation schedules. *Radiology*, 77, 940–947.

WINANS, L. F., DEWEY, W. C., and DETTOR, C. M., 1972. Repair of sublethal and potentially lethal X-ray damage in synchronous Chinese hampster cells. *Radiation Research*, *52*, 333-351.

Book reviews

Traité de Radiodiagnostic, Vol. 17–2. Stomatologie, pathologie maxillo-faciale", by P. Cernea; "Pathologie pharyngolaryngee", by G. Dulac, pp. ix+535, 1975, 595f.

This volume, written in French, deals with the radiology of the facial structures, oral cavities, pharynx and upper respiratory tract in considerable detail. The subject is presented in a simple, lucid and concise style which makes it suitable reading for the Fellowship examination, and it is profusely illustrated with well-chosen radiographs of excellent quality, each of which is accompanied by a detailed, labelled, line-drawing and a caption describing the important features being illustrated so that the book can be used as an atlas.

The text is well balanced, most space being given to the commonly-used conventional methods of examination. The importance of carefully performed tomography is stressed and amply illustrated. In addition, there are chapters on the use of radio-isotopes in the diagnosis of conditions of the salivary glands and on carotid and vertebral angiography, phlebography and lymphography. The chapter on arteriography is disappointingly brief in view of the fact that it is not uncommonly used in cranio-cervical conditions in some French centres, but this is offset by inclusion of selected references in this and in other chapters. The work is a good reference book with a detailed index.

B. KENDALL.

Atlas of Brain Anatomy for E.M.I. Scan. Prepared by Fred Shipps, Tony Madeira, Howard Huntington and Ray Wing, pp. 15, 1975 (Illinois, U.S.A., Charles C. Thomas), $6.00.

This book simply shows brains cut in horizontal sections in planes parallel to the orbitomeatal line and at 15 deg. to it at the levels commonly traversed by the E.M.I. Scanner. There are ten such sections, and the major structures shown on six of them are labelled on acetate overlays. There is also a chart showing coefficients of absorption. There is no text.

Unfortunately the labelling is not really extensive and detailed enough to be of value to any but the most uninitiated and one or two structures are labelled incorrectly.

Most neuroradiological departments using the scanner will already have made such sections for themselves, but there is undoubtedly a place for an atlas on similar lines, preferably combining anatomical sections with computed axial tomograms. This one cannot really be recommended in its present form.

B. KENDALL

The Superficial Veins of the Human Brain. By Henri M. Duvernay, pp. viii+110, 1975 (West Germany, Springer-Verlag), $35.90.

This book presents a detailed description and simple classification of the veins of the brain stem and base of the brain; it is based on a study of 50 beautifully prepared injected specimens and a review of the literature, much of which is recent and will be familiar to neuroradiologists.

Most of the book is taken up by an atlas of the expertly photographed and labelled specimens and there are diagrams depicting the more usual venous anatomy. The text is quite brief, but comprehensive and it is recommended as a source of anatomical reference for neuroscientists.

B. KENDALL.

1976, *British Journal of Radiology*, *49*, 200–201

Forthcoming events and other notices

The editors have decided that owing to the extreme shortage of space in the *British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and meetings announcements specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meetings announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

The following meetings is to be held at Institute House, 32 Welbeck Street, London W1M 7PG.

The Use of Hyperthermia and Non-Ionizing Radiation in the Treatment of Cancer, May 21, 1976

Further information from the General Secretary.

Radionuclides in Tumour Localization and Staging

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology is to be held at the Middlesex Hospital, London, W.1, on Wednesday, February 18, 1976.

Further information from the General Secretary, at 32 Welbeck Street, London, W.1.

Second-Stage Carcinoma of the Cervix

A meeting organized jointly by the Royal Society of Medicine, Section of Radiology, The British Institute of Radiology and the Royal College of Radiologists, to be held February 20, 1976.

For further information please contact Royal Society of Medicine, 1 Wimpole Street, London, W.1.

British Nuclear Medicine Society Annual Meeting

With the Hospital Physicists Association, is to be held on March 25–26, 1976, at the University of London Students Union, Malet Street, London, W.C.1.

Further information from Dr. D. N. Croft, Department of Nuclear Medicine, St. Thomas' Hospital, London SE1 7EH.

Annual Congress and Scientific Exhibition

To be held on April 8–9, 1976 at the University College, London. For information and registration please contact the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiology of Visceral Venous Obstruction

The Mackenzie Davidson Memorial Lecture, by Dr. M. Viamonte, Director of Radiology, University of Miami, School of Medicine, to be given at the University College, London, April 8, 1976.

Institute of Acoustics Spring Conference 1976

To be held at Engineering and Science Building, Liverpool Polytechnic, Byrom Street, Liverpool 3, April 12–14, 1976.

Contributions are invited and should be submitted to Dr. R. Lawrence, Principal Lecturer, Acoustics Group, Physics Department, Liverpool Polytechnic.

Further information and registration from The Secretary, Institute of Acoustics, 47 Belgrave Square, London SW1X 8QX.

Medical Images: Formation, Perception and Measurement

The Seventh L. H. Gray Conference, which will be concerned with the fundamentals of medical images, will be held at the University of Leeds, England, on April 13–15, 1976.

Address for further information: Dr. M. J. Day, Regional Medical Physics Department, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, England.

Postgraduate Course in Tomography of the Temporal Bone

To be held in Copenhagen, June 3–4, 1976. The course is sponsored by the I.C.R., the A.E.R. and the Scandinavian Association of Radiologists, and will be directed by Dr. Sam Brünner, president of the Congress.

For further information and registration, please contact Dr. Paul E. Andersen, Department of Radiology, University Hospital, 5000 Odense, Denmark.

Health Physics Summer School

The 17th annual Summer School in Health Physics (Radiation Protection) will be held at Imperial College from June 21 to July 2, 1976.

Initial enquiries should be sent to Dr. H. D. Evans, Department of Chemical Engineering, Imperial College, London SW7 2AZ.

Computers in Radiotherapy in Europe

It is proposed to hold a Workshop at IAEA, Vienna on July 5–10, 1976, organized by the Groupe Informatique, A.E.R. with the support of the European Association of Radiology. The aim will be to establish the contribution that the computer makes at the clinical level in the fields of dose computation, clinical records, radiobiology, etc., and to determine future development.

Further information from Dr. D. N. Edwards, Clinical Research Unit, Mersey Regional Centre for Radiotherapy and Oncology, Clatterbridge Hospital, Bebington, Wirral, Merseyside L63 4JY, U.K.; or Dr. T. Moller, Radioterapikliniken, Lasarettet, S-221 85 Lund, Sweden.

Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV International Congress of Radiology

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colégio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Radiochemistry Publications

The Technical Information Centre of the United States Energy Research and Development Administration publishes a series of monographs of radiochemistry and radiochemical techniques, including for example:

Rapid Radiochemical Separations
Paper Chromatographic procedures and
Processing of Counting Data.

The minimum price is $3.00 for either one, two or three randomly selected publications.

Further details from National Technical Information Service, U.S. Department of Commerce, Springfield, Virginia 22161, U.S.A.

Forthcoming events and other notices

MIRD PUBLICATIONS

Medical Internal Radiation Dose Committee (MIRD) has announced the availability of the following two new publications:

Pamphlet 10. *Radionuclide Decay Schemes and Nuclear Parameters for Use in Radiation-Dose estimation.*

Pamphlet 11. *"S" Absorbed dose per unit Cumulated activity for Selected Radionuclides and Organs.*

We hope to publish reviews in the near future.

The Royal College of Radiologists: Recommendations on the implementation of "The 10-Day Rule"

The Code of Practice for the Protection of Persons against Ionizing Radiations Arising from Medical and Dental Use should be accepted as a basis for reasonable practice. It states that in *all* female patients of reproductive capacity in order to reduce the likelihood of irradiation of a pregnancy:

(1) the clinician requesting the examination should consider the possibility of an early stage of pregnancy (para. 7.3.1);
(2) the date of the last menstrual period should be entered on the request form and it is the responsibility of the clinician requesting the examination to ask for this (para. 7.3.1);
(3) examination of the lower abdomen should, if praticable, be carried out within the ten days following the first day of the menstrual cycle (para. 7.3.1);
(4) if there is any doubt about the advisability of carrying out an investigation or the nature of the investigation required, the matter should be resolved by consultation between the medical officers responsible respectively for the clinical and radiological care of the patient (para. 7.2.3).

RESPONSIBILITY

There is a chain of responsibility. The patient herself, the referring clinician, the radiologist and staff of the X-ray department all have a duty to ensure, as far as possible, that the fetus *in utero* is not exposed to ionizing radiations without adequate reasons.

Referring clinician

The referring clinician takes the prime responsibility for initiating the examination. He should:

(1) be satisfied that the result of the examination may affect the management of the patient;
(2) weigh the risk against the possible benefit;
(3) state the clinical indication, the provisional diagnosis and information required (para. 7.2.2);
(4) give the stated date of the first day of the last menstrual period (LMP); (all X-ray request forms should have a space marked "LMP" so that the clinician is constantly reminded of his duty);
(5) state whether the ten-day rule is to be "observed" or "ignored";
(6) sign the form so that it is clear who he is and what position he holds.

Staff of X-ray Department

Examination on day of request. The last opportunity to consider the ten-day rule falls on the staff of the X-ray department. The receptionist or radiographer should check the date of the LMP and note whether the ten-day rule is to be "observed" or "ignored". If the ten-day rule is to be ignored or the day falls within the first ten days following the first day of the last menstrual cycle, the examination is carried out.

Booked examinations. If the ten-day rule is to be "observed", the booking-clerk should explain to the patient that the examination can be carried out only on the ten days following the first day of the menstrual cycle and book the examination accordingly. When the patient returns for her X-ray examination, the radiologist or radiographer should check that the predicted menstrual period did in fact occur.

Patient

(1) The implication of the questions concerning the ten-day rule should be made known to the patient.
(2) The patient bears a responsibility to give accurate information concerning the possibility of a current pregnancy and the details of her menstrual cycle.
(3) Hospital authorities should take steps to remind patients of the risks of X rays during pregnancy. For example, by notices in the out-patients such as "Some X-ray examinations during pregnancy may be harmful. If you could be pregnant, you should tell the doctor" or in female changing rooms in the X-ray department, "If you are pregnant or think you may be, please inform the radiographer *before* you are X rayed".

PATIENTS AFFECTED

Patients at risk include all females in the child-bearing age 12–50 years except:

(1) women who deny recent sexual intercourse;
(2) women who are menstruating at the time;
(3) women on a contraceptive pill who are satisfied that it has proved effective over a period of not less than three months;
(4) women who have had an intra-uterine contraceptive device for over three months and have found it to be effective;
(5) where there has been a hysterectomy or other sterilizing procedure.

Problems include:

(a) patients whose mental state suggests that they are incapable of appreciating the nature of the issue involved;
(b) persons whose language difficulties make communications difficult (an explanation of the issues involved and a consent form in foreign languages would be of value);
(c) Patients with irregular menstruation.

The Royal College of Radiologists: Recommendations on the implementation of "The 10-Day Rule."

TYPES OF EXAMINATION

Any radiological examination involving the abdomen or pelvis is potentially dangerous.

EXAMINATIONS TO BE AVOIDED.

Barium enema
Barium meal
Intravenous urogram
Cystogram
Cholecystogram
Lumbar spine, pelvis and hips
Abdominal angiography

SPECIAL PROBLEMS

Patients from accident and emergency

Many patients from "A and E" departments are neither accidents nor emergencies. Each case must be considered on its merits. The ten-day rule should be observed unless there is an overriding clinical indication for immediate examination.

Out-patients

The main difficulty arises when there are long waiting lists for radiological examinations. Because of the confidential nature of the enquiries made by the booking clerk, privacy is essential. The clerk will require special training in her duties. The employing authority may have to authorize extra clerical staff to cover these responsible duties.

Ward patients

The organization and economics of hospital practice make it particularly difficult to implement the ten-day rule for in-patients.

Emergency admission

In most instances, the ten-day rule can be ignored on grounds of clinical urgency.

J. W. LAWS,
REGISTRAR

British Institute of Radiology Fractionation Working Party: A new clinical trial

The laryngo-pharynx clinical trial of three fractions per week versus five fractions per week was officially concluded on December 31, 1975. Over 700 cases were entered into the trial from 18 radiotherapy centres. Further interim results will be summarized in the Sixth Progress Report which is in preparation. The follow-up of these patients will of course continue to the tenth year after treatment.

A new laryngo-pharynx clinical trial started on January 1, 1976 to compare short overall treatment times (three to four weeks) with long overall times (six to seven weeks). Both long and short schedules will be compared in each participating centre.

G.W. and J.F.F.

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The Department of Diagnostic Radiology, University Hospitals in Lund and Malmö
presents a course in

Angiography of Abdominal and Retroperitoneal Structures

June 11–15, 1976

University Hospital, Lund, Sweden

Chairman: Olle Olsson, M.D.

General information:
The course will be held in the English language and is limited to 200 participants. It is designed for radiologists with basic knowledge in abdominal angiography. This first course will include angiographic technique, indications and ethical aspects, in half-day lectures and afternoon film reading seminars.

Faculty:
Herbert L. Abrams, M.D., Professor and Chairman, Department of Radiology, Harvard Medical School, Boston, Massachusetts, U.S.A.
Stanley Baum, M.D., Professor and Chairman, Department of Radiology, The Hospital of the University of Pennsylvania, Philadelphia, U.S.A.
Stewart R. Reuter, M.D., Professor, Department of Radiology, University of Michigan, Ann Arbor, Michigan, U.S.A.
Mark Wholey, M.D., Professor and Chairman, Department of Radiology, Shadyside Hospital, Pittsburgh, Pennsylvania, U.S.A.
Olle Olsson, M.D., Professor and Chairman, Department of Diagnostic Radiology, University Hospital, Lund, Sweden.
Erik Boijsen, M.D., Professor and Chairman, Department of Diagnostic Radiology, Malmö Allmänna Sjukhus, University of Lund, Sweden.
Bo Jacobsson, M.D., Associate Professor, Department of Radiology, University Hospital of Gothenburg, Sweden.
Christer Owman, M.D., Professor, Department of Histology, University of Lund, Sweden.
Anders Lunderquist, M.D., Head of the angiographic section, University Hospital, Lund, Sweden.
Staff members of the University Hospitals in Lund and Malmö.

The course is sponsored by the European Association of Radiology and the Swedish Society of Medical Radiology.

Information about the course can be obtained from Anders Lunderquist, M.D., Department of Diagnostic Radiology, University Hospital, S-221 85 LUND, Sweden.

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Printed in Great Britain by Lund Humphries
London and Bradford
Published by The British Institute of Radiology
32 Welbeck Street, London W1M 7PG

ISSN 0005–1285

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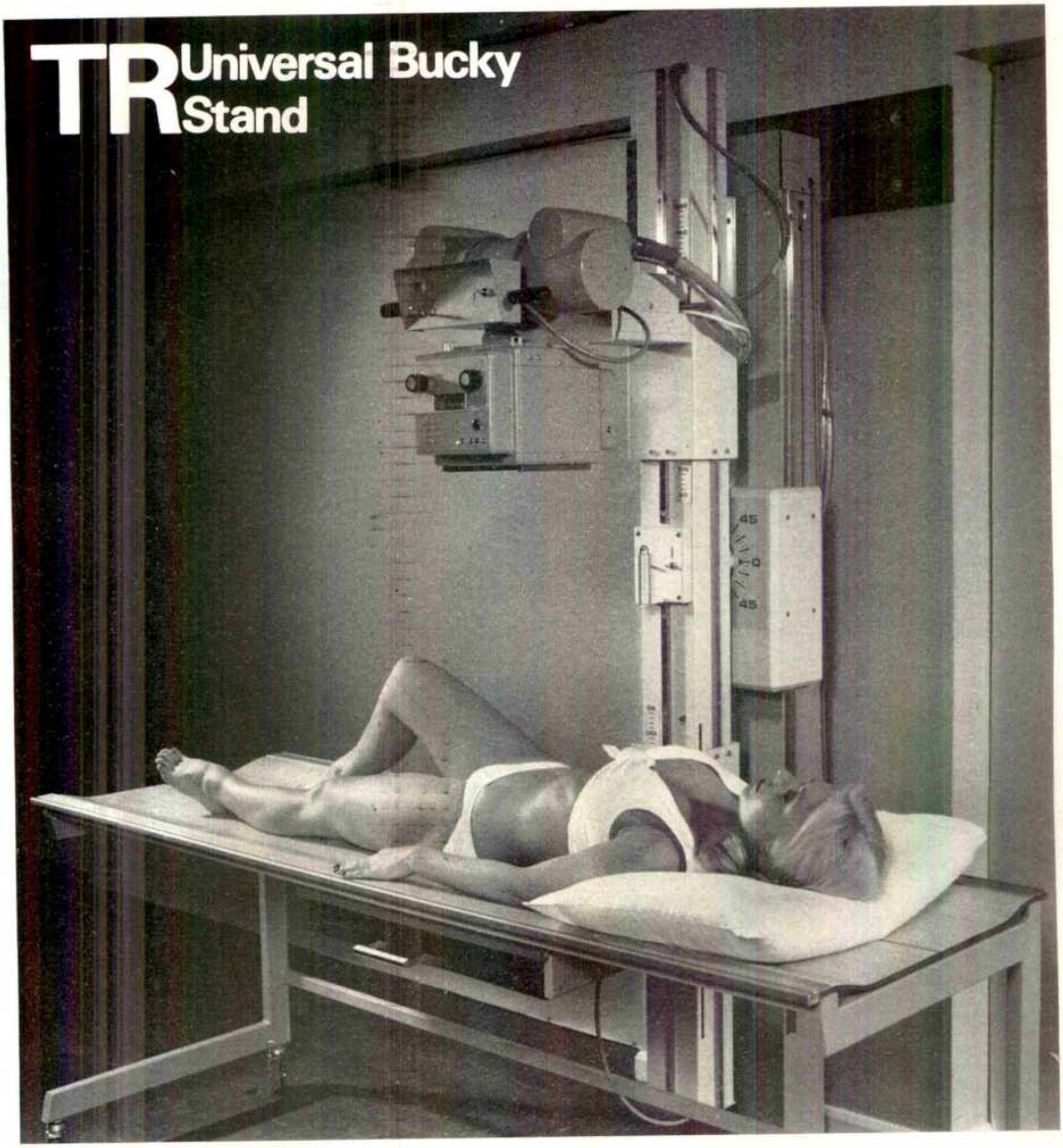

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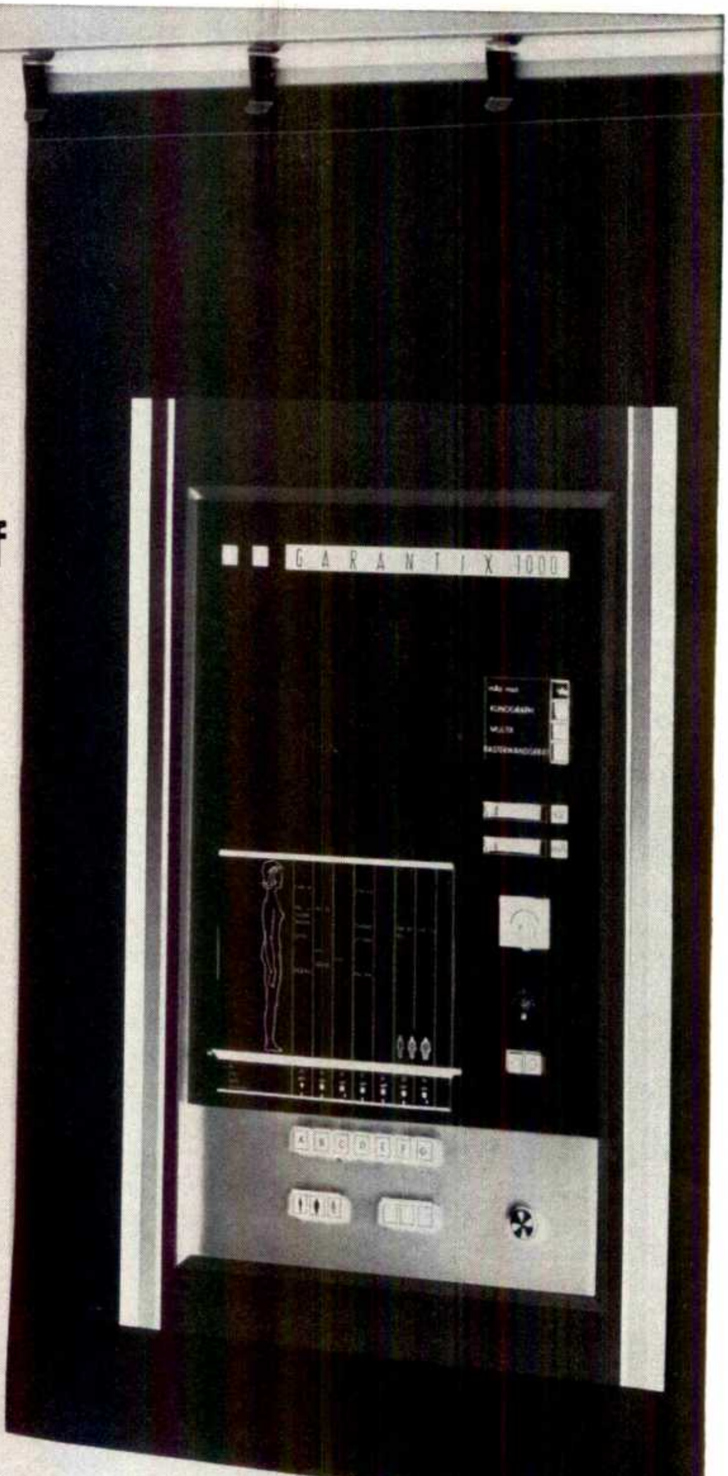

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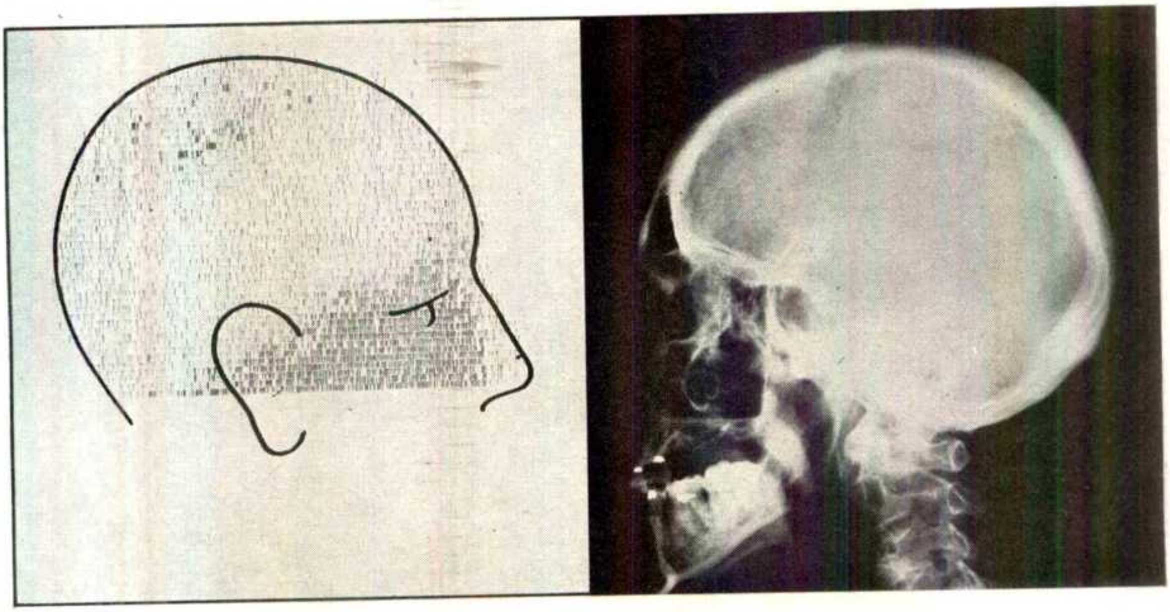

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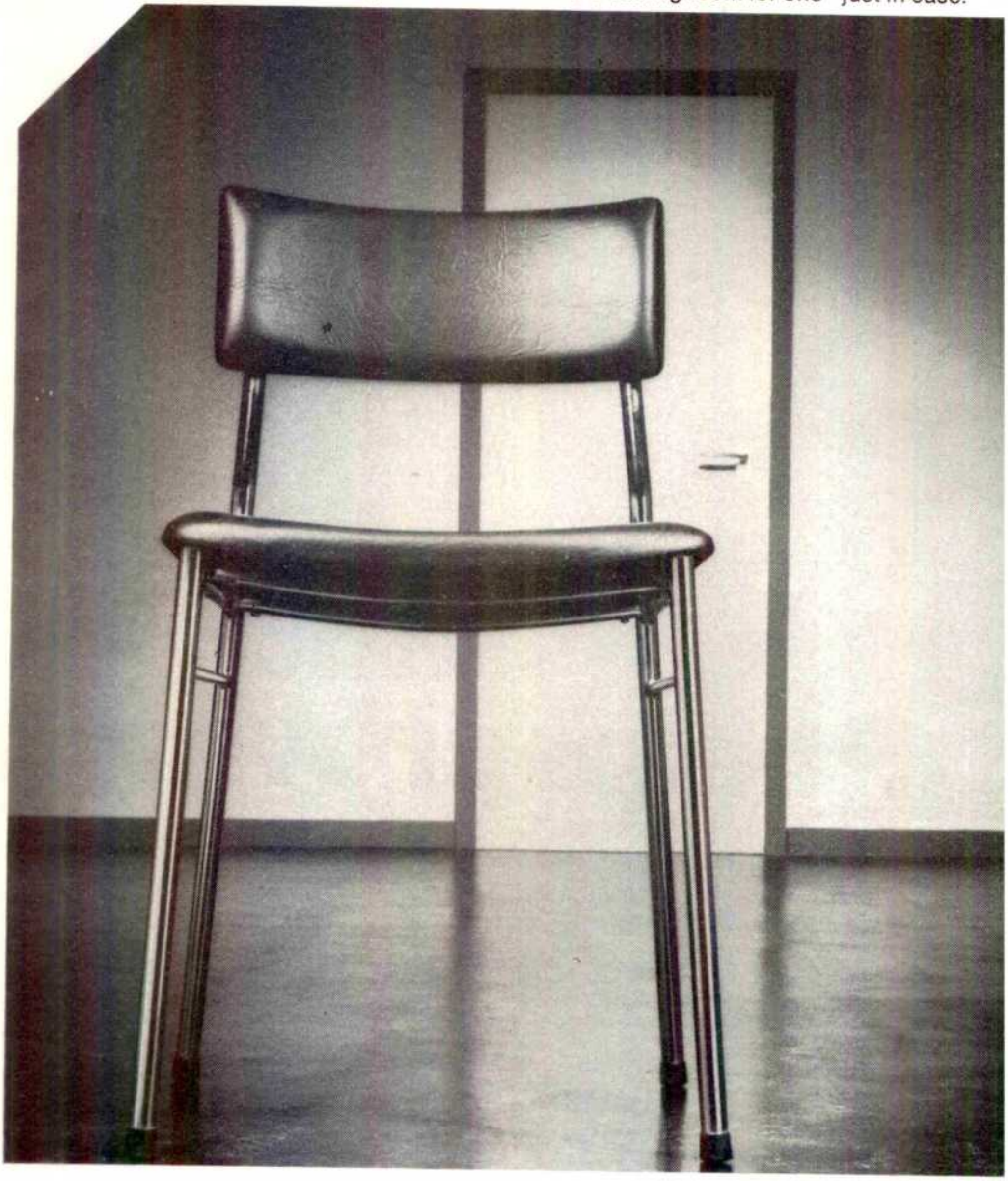

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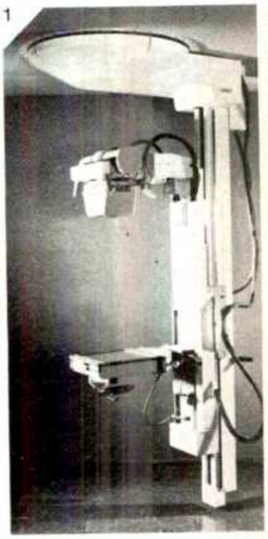

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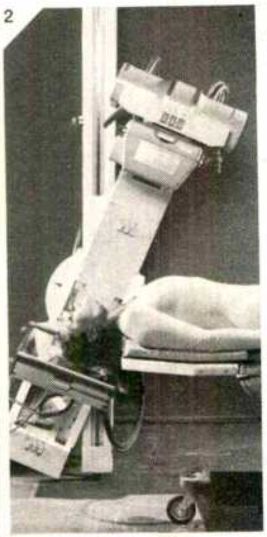

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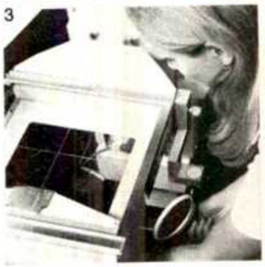

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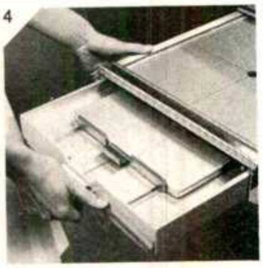

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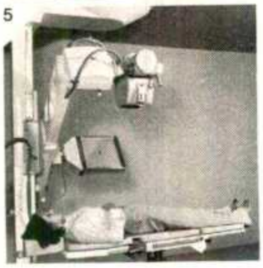

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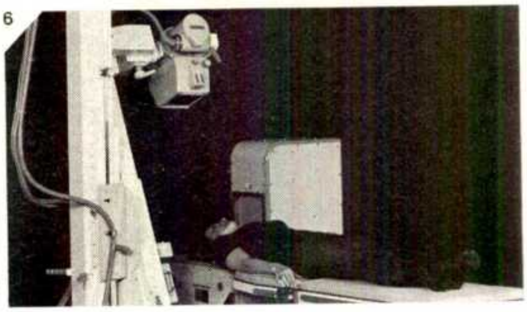

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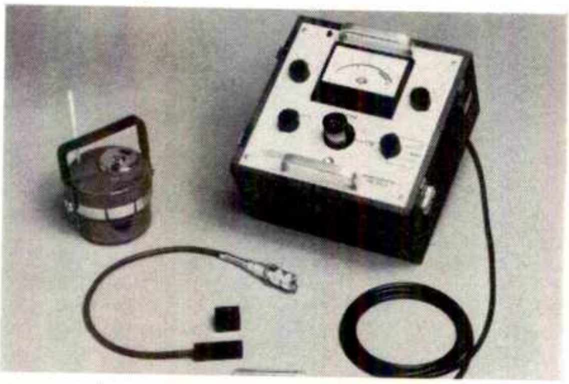

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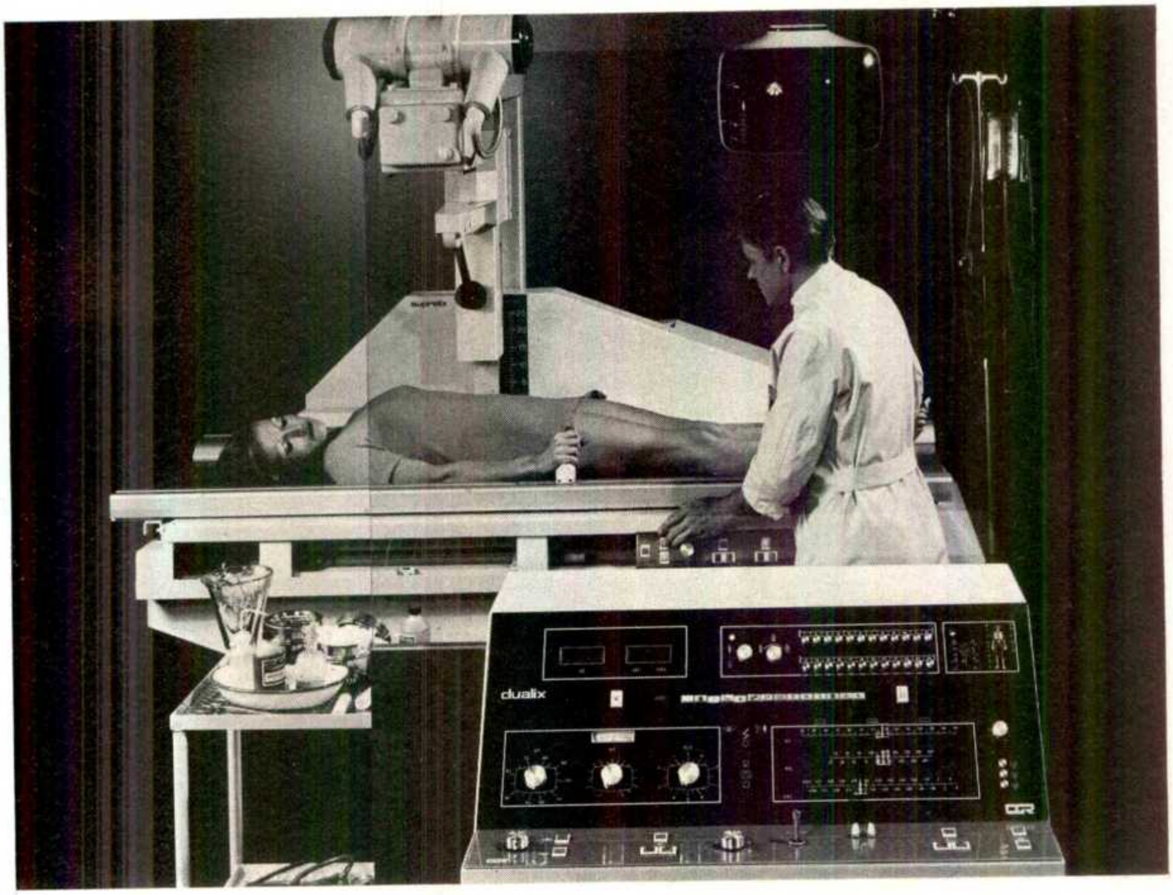

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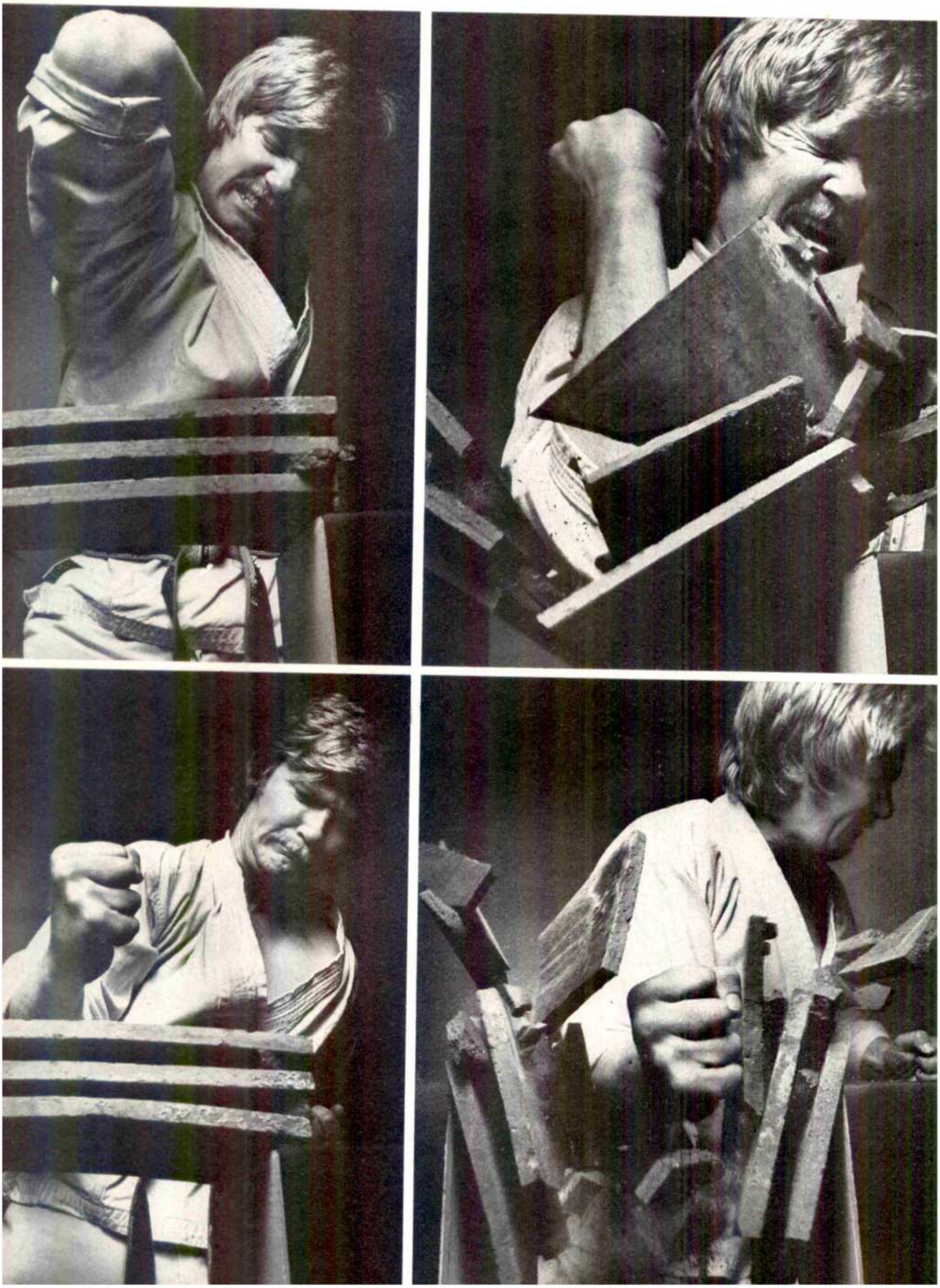

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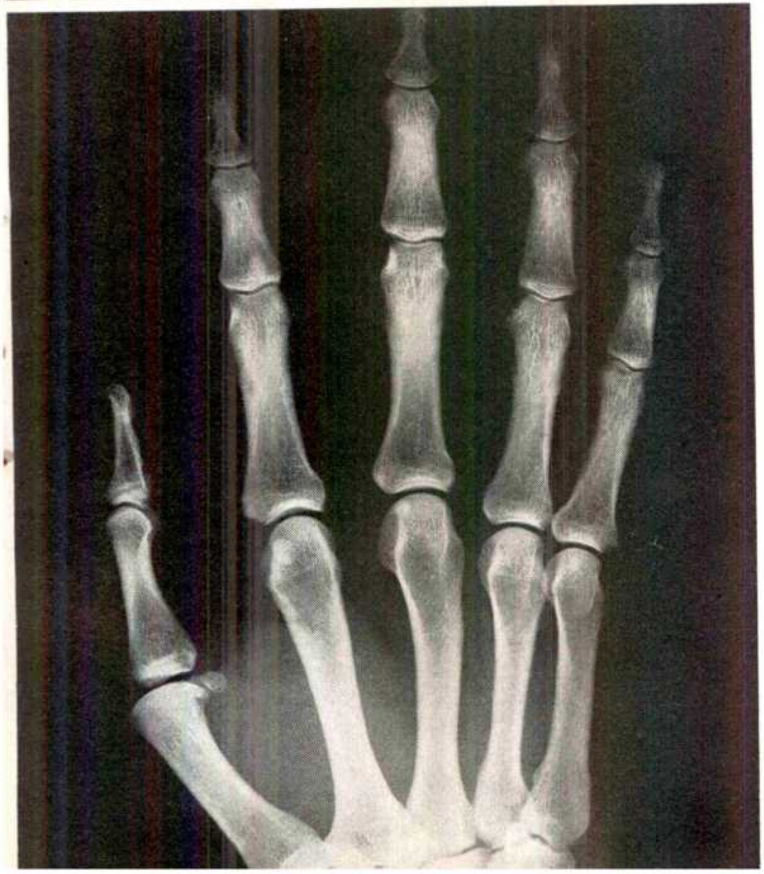

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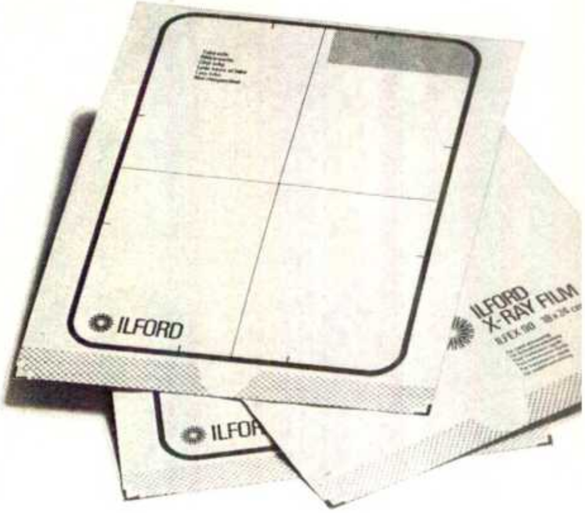

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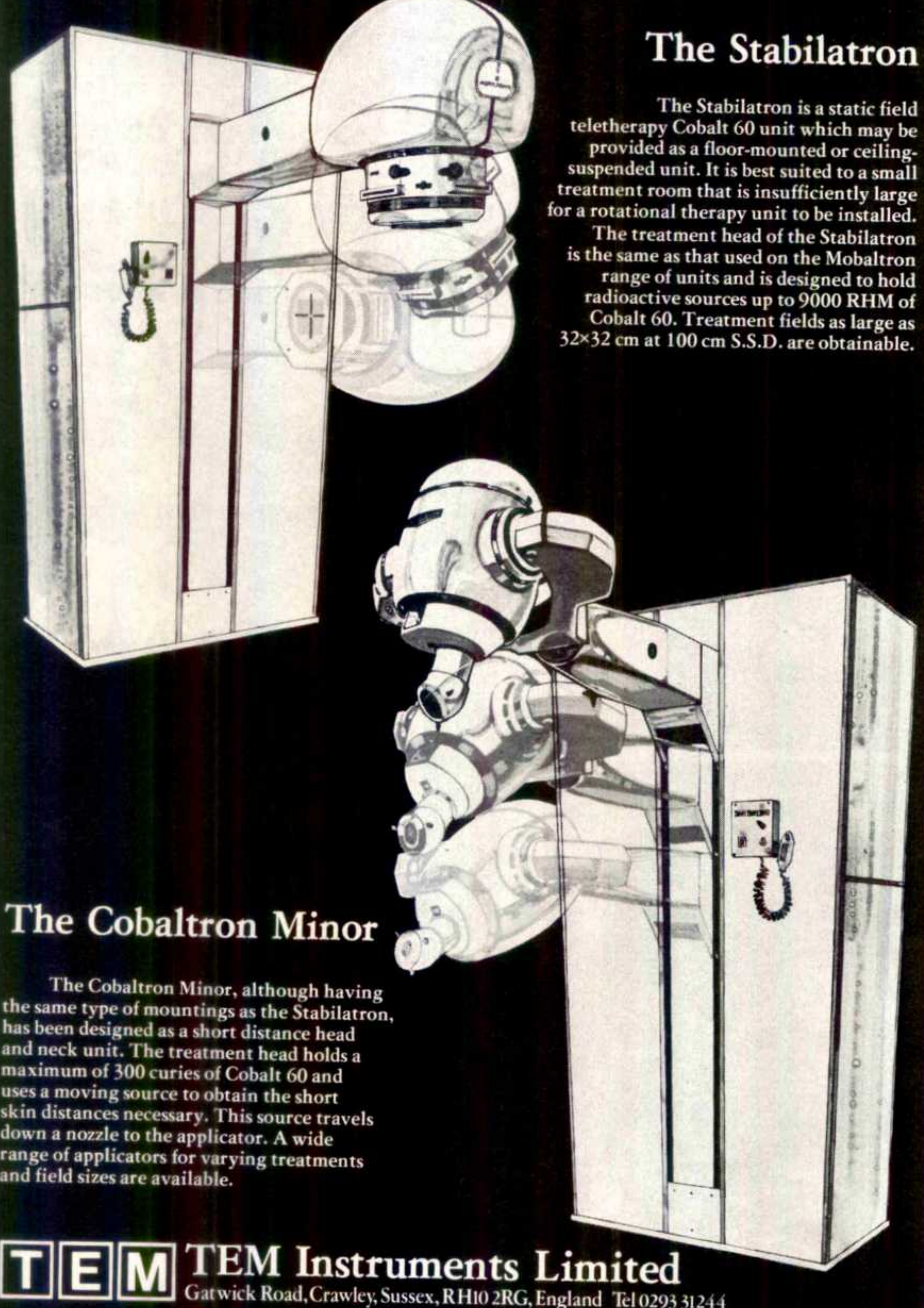

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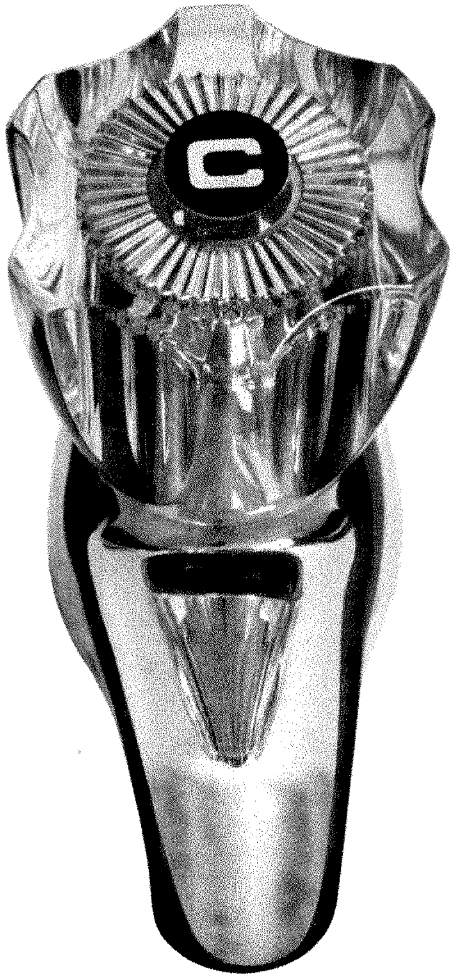

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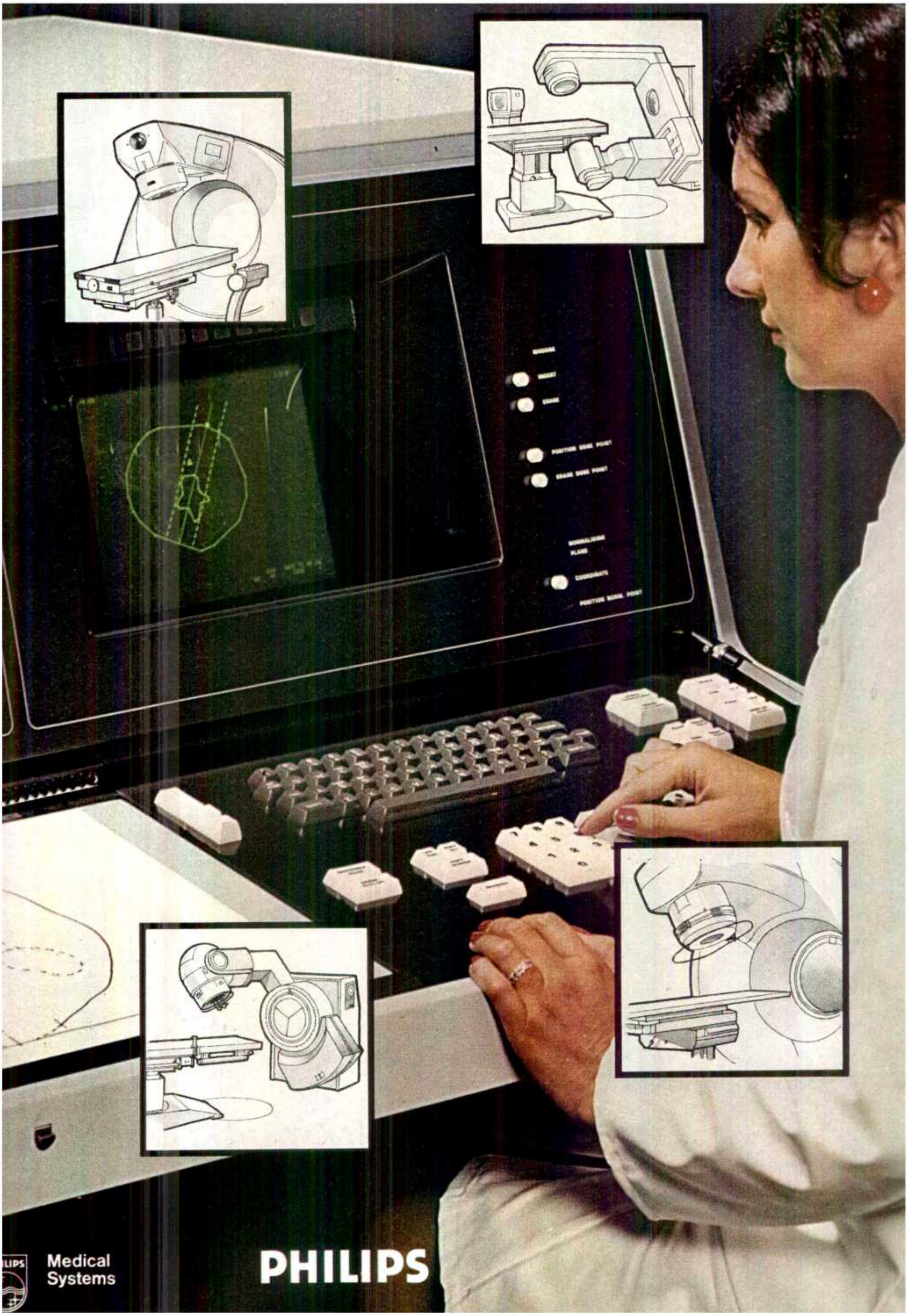
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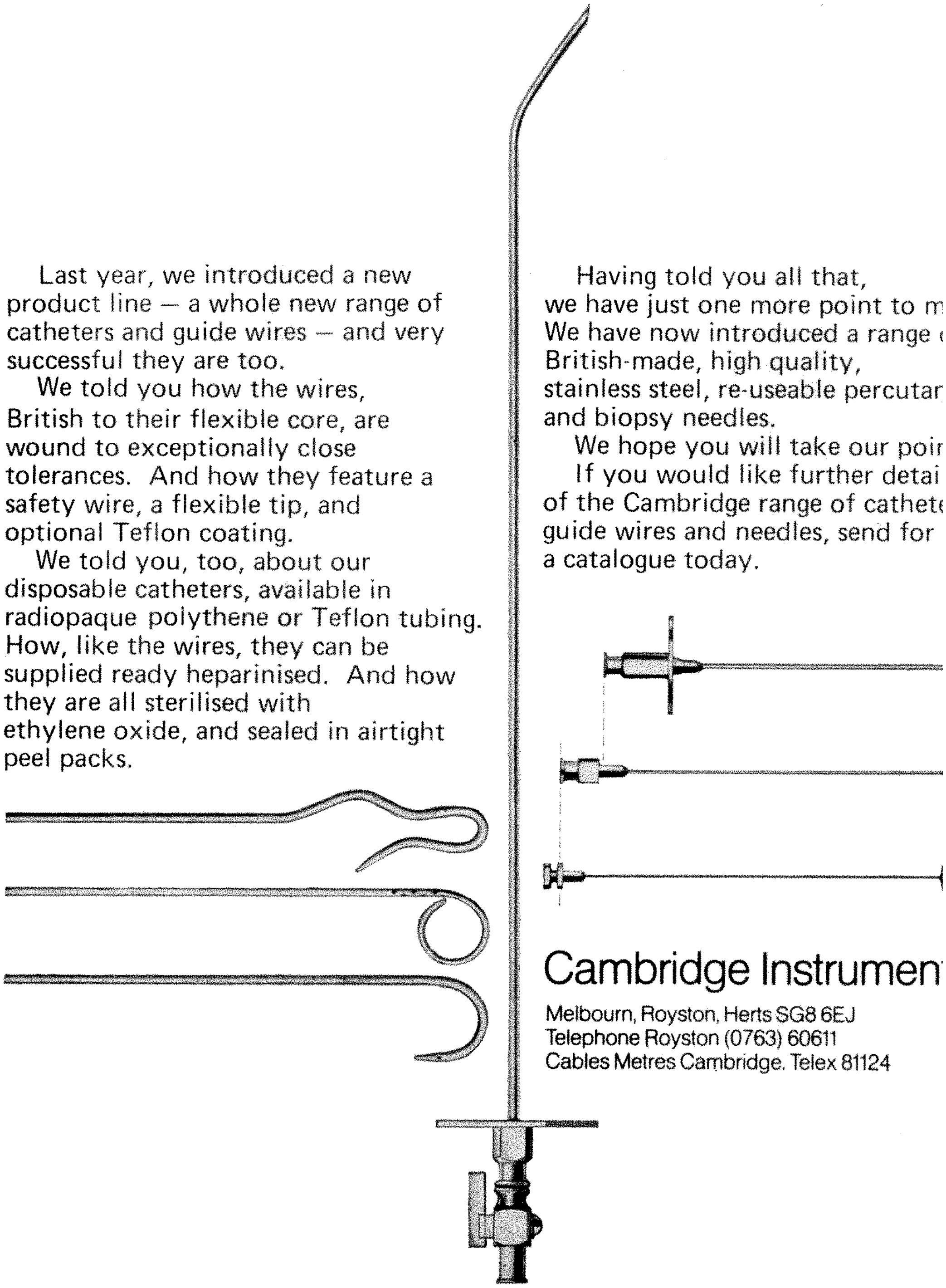

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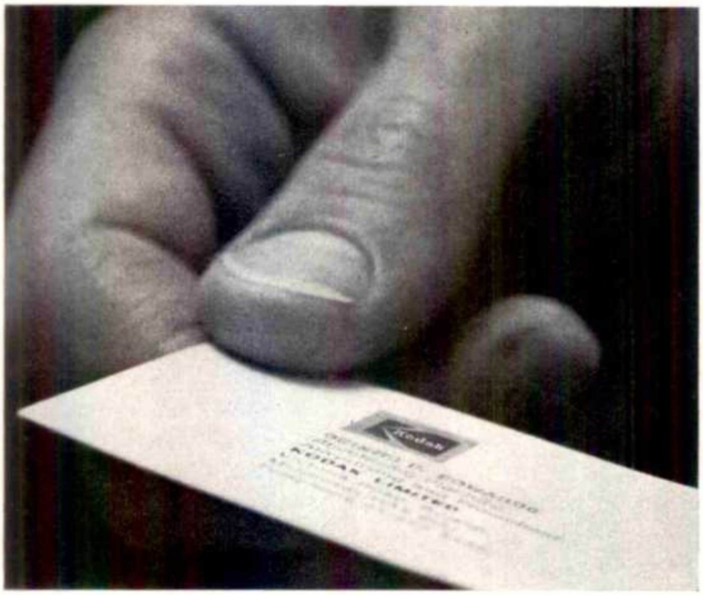

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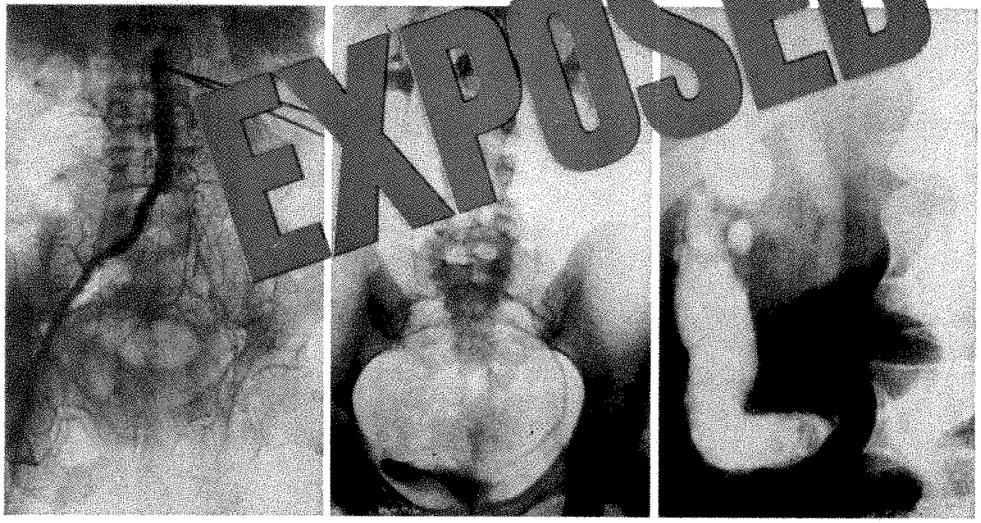

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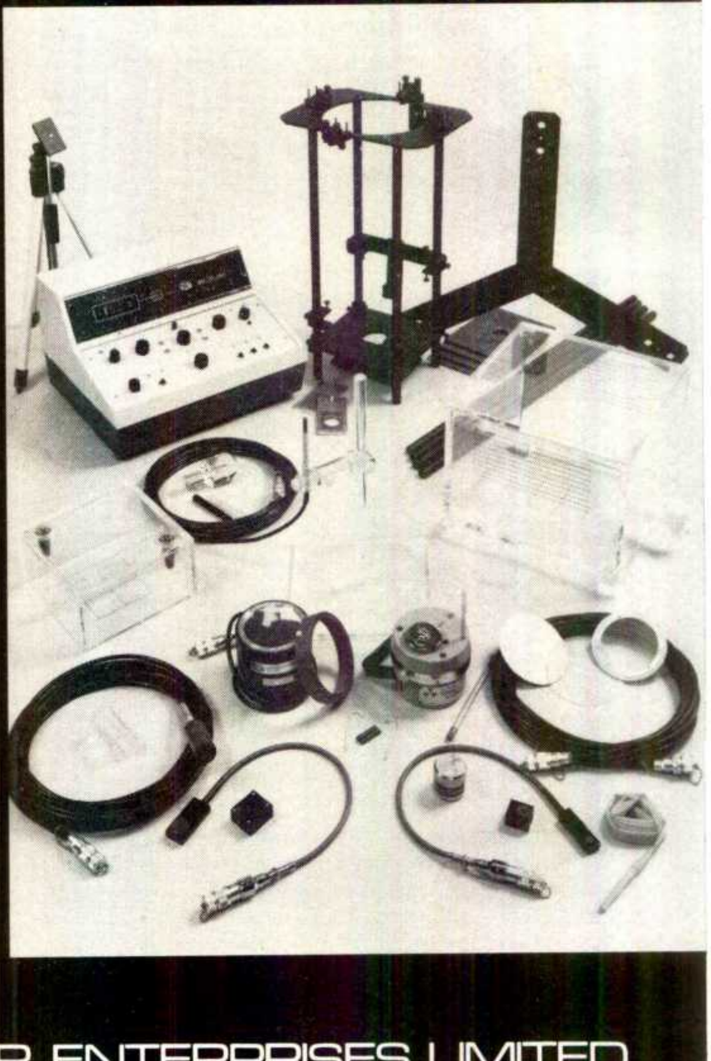

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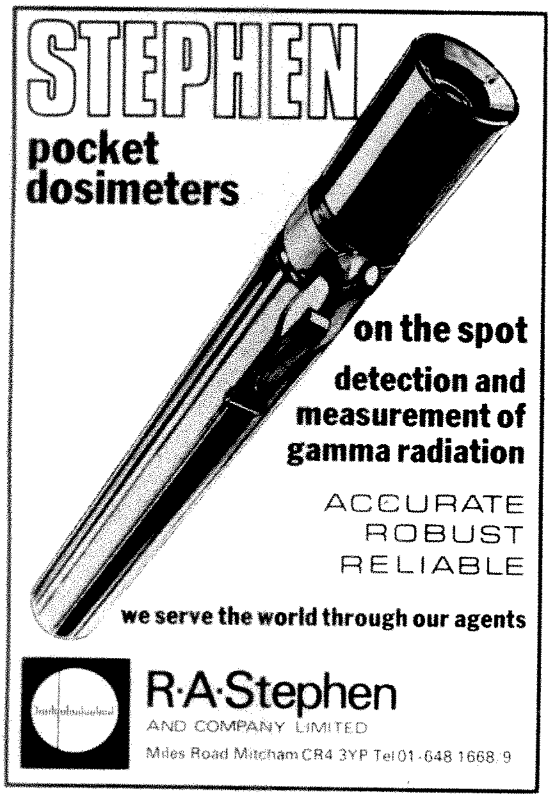

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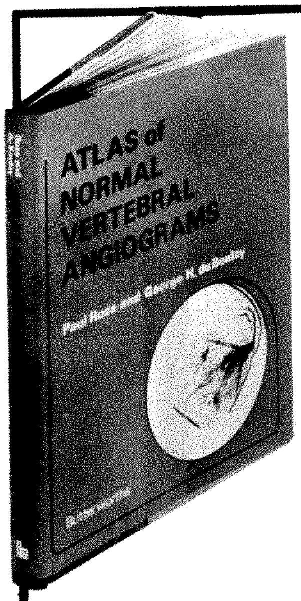
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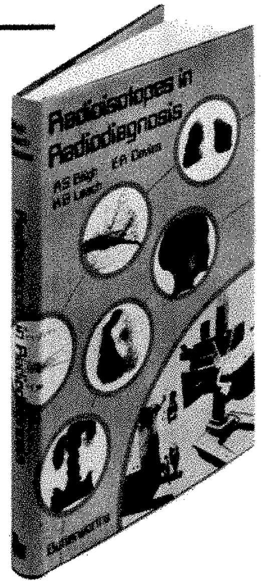

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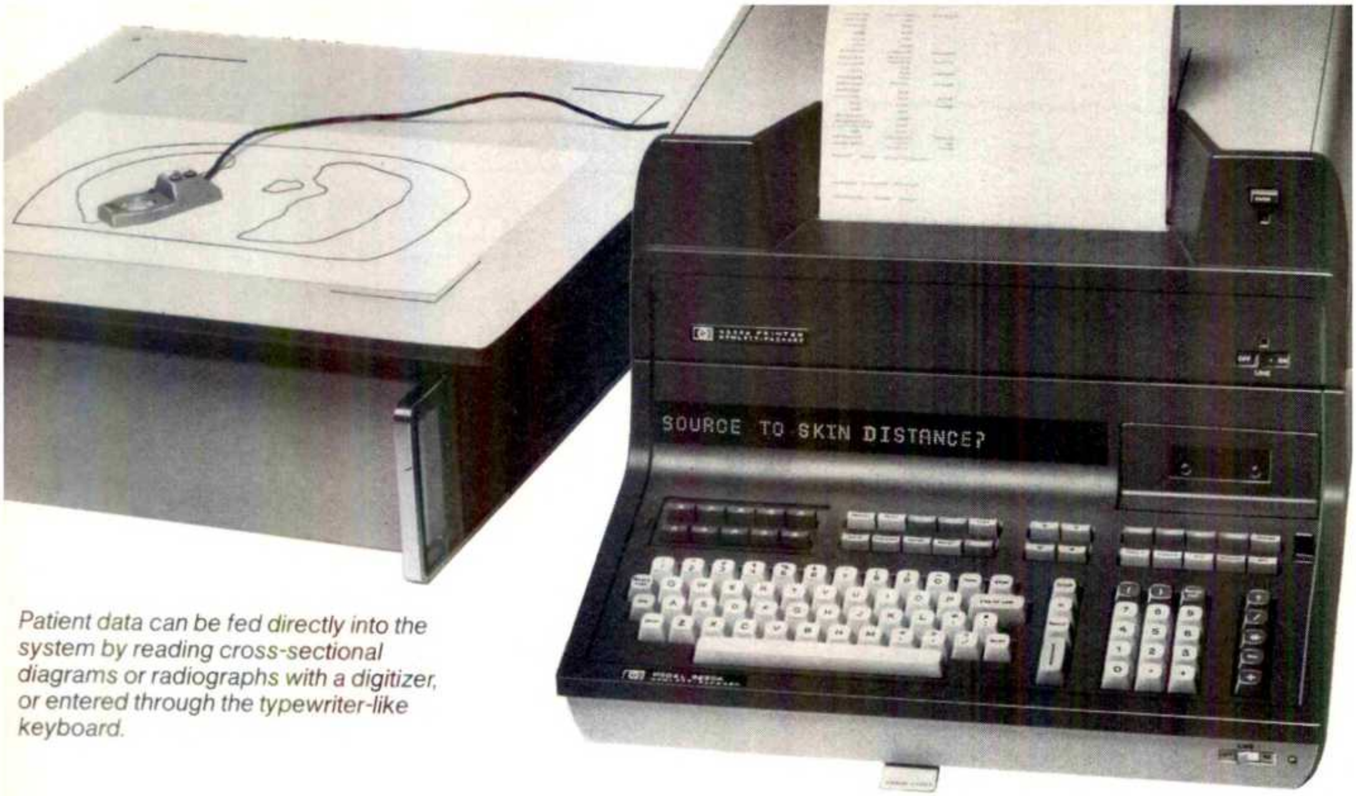

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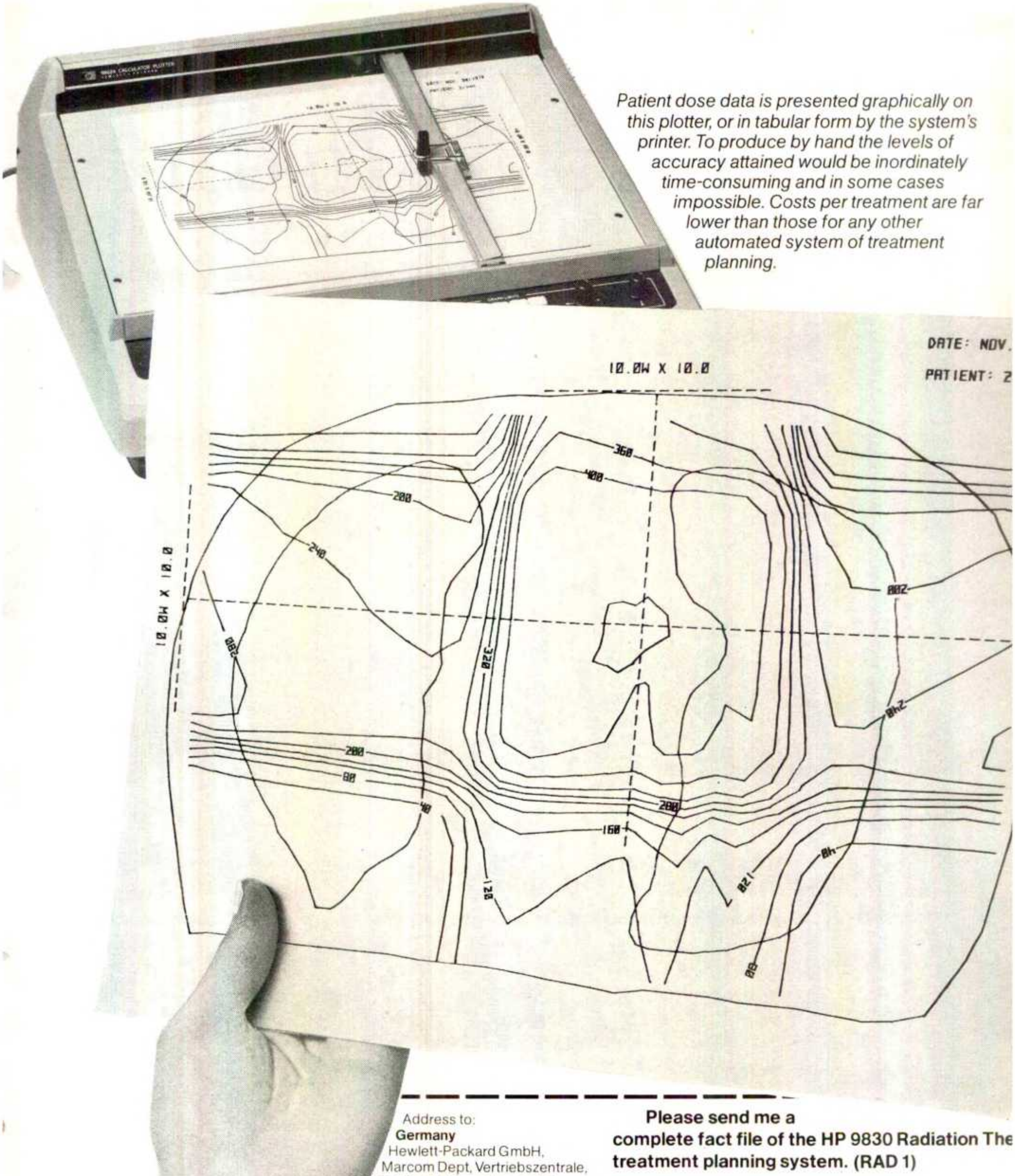

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Applications of Modern Technology in Radiotherapy

We are pleased to announce the publication of this report on treatment simulators. The report discusses the uses of simulators in radiotherapy and sets out guide-lines for their future development, both in the specifications of design parameters and in techniques for use. The specifications of simulators currently available from a number of manufacturers are tabulated and compared with those considered desirable by the authors.

The authors point out that the simulator has been a radiotherapy aid for a quarter of a century, but that to many its purpose and use are still undefined; they take the view that although verification is an important function of a treatment simulator, its main function is the accurate localization of the tissues in the region to be treated.

This Report is one of several now in preparation under the general title *Applications of Modern Technology in Radiotherapy.* The authors were brought together as a working group following discussions between members of The British Institute of Radiology, the former Faculty of Radiologists, the Hospital Physicists Association and The Society of Radiographers on the general need for information and guidance on the most effective ways of bringing new advances in technology into wide use in radiotherapy. We believe that this first report will prove of considerable interest to many present and prospective users of treatment simulators in Great Britain and in many other countries.

Members of the working group:
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1976, *British Journal of Radiology*, 49, 203–205
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The British Journal of Radiology

Radiology now

Fast neutrons—clinical requirements*

For decades, there have been numerous treatments for cancer and recently a plethora of drugs has added almost limitless possibilities to these. When fast neutrons became available clinically, there was, understandably, a demand for their effects to be compared objectively with conventional radiation.

The precision and efficiency of modern megavoltage X- and γ-ray machines, and their ability to deliver an exact dose of radiation to the volume delineated, probably cannot be improved upon, and usually exceeds the ability of the clinician to localize the extent of the malignancy. Output of radiation is so good that treatment times are of the order of one to three minutes, and well-defined beams can be directed in any direction and in any plane. Patients can be treated in the most suitable of many possible positions and do not usually suffer skin reactions. Megavoltage machines are situated within hospitals and are available in most centres throughout the world where physicists and clinicians have wide experience in their use.

In contrast, all existing neutron sources suffer from serious disadvantages. For instance, in the U.S.A., patients from the M.D. Anderson Hospital are transported 100 miles into Texas for each treatment. The M.R.C. Cyclotron in Hammersmith Hospital has a neutron beam which is fixed in the horizontal position and is collimated in squares or rectangles of fixed sizes. The energy (7·5 MeV) gives a dose distribution only slightly better than 250 kV X rays and the isodoses are rounded at the ends and show a clinically significant penumbra. Skin reactions are produced which proceed to moist desquamation before healing. Because of its poor penetration, pelvic and abdominal tumours are not treated except in very thin patients. Even in these, the dose distribution is uneven and compares badly with that from ^{60}Co. Tumours of the head and neck can be given a more uniform dose, but because of the wide penumbra and rounding of the isodoses, it is difficult to avoid the spinal cord. Damage to the cord may, therefore, be due more to the poor collimation of the beam than to a specific effect of neutrons on central nervous tissue.

Despite these disadvantages, in the one controlled clinical trial where statistically significant results are available, the neutron-treated patients showed a highly significant benefit over those treated with photons (Catterall *et al.*, 1975). In other comparative studies at Hammersmith, where patients had two or more identical tumours, one treated with neutrons and the other with photons, the neutron-treated tumours always did better, in terms of not recurring after treatment for the same degree of early and late normal tissue reaction. In no case has a neutron-treated tumour ever shown less regression than a similar tumour treated with photons, nor has this advantage been obtained at the cost of unacceptable damage to normal tissues.

There are now increasing demands from many centres all over the world for fast neutrons to treat patients. This demand is being met by the conversion of cyclotrons constructed for other purposes, essentially unsuitable for clinical work, or by the production of neutron machines which technically fall far short of modern megavoltage X-ray machines. There is, therefore, a great risk that information obtained will be misleading, because the clinical results could reflect more the inadequacy of the delivery of neutrons to the tumour than the effects of neutrons themselves.

Six years' experience of treating patients with fast neutrons, suggest six factors which must be included in the production of a neutron machine suitable for treating patients in a comparable way with photons from the megavoltage machines now in routine use throughout the world.

---

*Reprint requests to: Mary Catterall, F.R.C.R., Consultant in Charge, Fast Neutron Clinic, M.R.C. Cyclotron Unit, Hammersmith Hospital, London W12 0HS.

1. *The beam must always be available to meet clinical requirements*

The total dose must be given in the number of fractions and overall time which were selected at the outset.

Unreliability of neutron output leads to erratic treatments and makes the accurate assessments of effects impossible, thereby lessening the value of clinical research. This was the main reason why Stone (1942 and 1948) never established a satisfactory treatment régime in his early trial of neutron therapy. Unreliability is traumatic to patients, who suffer disappointment and anxiety when their treatments cannot be given, and tumours may continue to grow. The reputation of the unit suffers, and clinical colleagues grow sceptical about referring patients for treatment.

Clinical requirements must have first priority. Competing claims for machine time or high cost of renting time can be reasons for administrators to withhold funds, causing interruptions to a clinical programme.

2. *The output must give treatment times not exceeding four minutes*

For comparison with photons, treatments must be given within a few minutes, otherwise factors such as increased stress may influence the results. Prolonged treatment times select patients who can maintain a certain position for the time demanded, and make some positions impossible. Long treatments may be given in the supine position, but this excludes patients in pain or with co-existing disorders such as congestive heart failure.

3. *Depth dose and isodose shape must be at least as good as those of ^{60}Co*

One of the most useful advances in the treatment of cancer was the advent of megavoltage beams of radiation with their increased penetration and sharply cut-off edges, enabling more uniform doses to be delivered to deep-seated tumours while adjacent normal structures could be more easily avoided. Neutron beams must be comparable at least with those of ^{60}Co. Less penetrating radiation makes planning of an ideal treatment impossible, increases the risk of delivering high doses to vulnerable normal structures such as the spinal cord, and restricts treatable tumours to those in superficial sites.

4. *The neutron machine must be within a hospital*

If the machine is outside a hospital, the necessity of travel to it selects patients who can undertake the journey. The time, expense and distance may influence the total number of treatments given, or the fractionation per week, and may result in an inferior overall treatment. Radiotherapy departments for photon treatment are part of a hospital, and all other necessary medical and surgical treatments are readily available to the patients. If long distances or unusual surroundings are involved for neutron treatments, they will usually have a deleterious effect, and will certainly be different from the photon-treated patients. These factors would have to be considered in the results of controlled clinical trials.

5. *The set-up of neutron treatments must not be compromised*

Any of the following will put neutron treatments at a disadvantage compared with those from megavoltage photon machines.

(a) Radiation hazard in the treatment room. If this level is higher than permissible, treatment set-ups and the precise positioning of the patient relative to the beam will be hurried, and parts of the tumour may be inadequately covered.

(b) Collimators which are so heavy that they cannot be easily handled or quickly changed.

(c) Fields of fixed sizes and shapes where it is impossible to shield normal structures from radiation. (b) and (c) are particularly sophisticated and precise with photon treatments, and clearly add significantly to the protection of normal structures which would otherwise be irradiated. A higher rate of complications is likely with neutrons, not because of an inherent property of neutrons, but because of the inferior delivery of dose to the tumour.

(d) Limitation of time available for treatments on the machine. This can lead to hurried set-ups, with less care and precision being taken on neutron treatments than is available for photon treatments.

6. *The beam should not be fixed in one position*

Megavoltage radiation can be given through 360 deg. and through fields oblique to the long axis of the body. These are assets which assist in planning and in the treatment of patients whose general condition puts restrictions on their position. With highly developed techniques, patience and experience, we have found the fixed horizontal beam at Hammersmith to be much less of a difficulty than the low energy of the beam. However, with a higher energy beam, it would be preferable, probably essential, to have the beam vertical, if only one position were possible.

Beam positions in the vertical and horizontal are the minimum requirement of a new machine; isocentricity is required if it is to be truly comparable with a megavoltage machine.

Conclusion

The M.R.C. Cyclotron is reliable and ideally sited within the grounds of Hammersmith Hospital, but it is grossly inferior technically to the megavoltage photon machines used for treating comparable patients. So marked are the differences, that if the clinical results obtained with this neutron beam had been inferior to the photon results, they could not have been said to have proved the case against neutrons. But, despite the technical problems, the results are showing advantages to the neutron treated patients and make it necessary to discover precisely which tumours should be treated with neutrons. Provisions will then have to be made to give such treatments in other centres.

To do this, neutron treatments must be made comparable, in all six aspects described, with those from megavoltage machines. In the long term the conversion of cyclotrons, originally constructed for other purposes and essentially unsuitable for the treatment of patients, would not be as economical as the production of a neutron source designed specifically for clinical use.

Mary Catterall.

REFERENCES

Catterall, M., Sutherland, I., and Bewley, D. K., 1975. First results of a randomised clinical trial of fast neutrons compared with X or gamma rays in the treatment of advanced tumours of the head and neck. *British Medical Journal*, *2*, 653–656.

Stone, R. S., 1948. Neutron therapy and specific ionization. *American Journal of Roentgenology*, *59*, 771–785.

Stone, R. S., and Larkin, J. C., 1942. Treatment of cancer with fast neutrons. *Radiology*, *39*, 608–620.

Book review

Manual on Radiation Protection in Hospitals and General Practice. Volume 2 Unsealed Sources. By D. Frost and H. Jammet, pp. 113, 1975 (Geneva, sponsored by the I.L.O., I.A.E.A. and W.H.O.), Sw.Fr.24.

Although the problems of radiation protection have been covered for the atomic energy industry, it was felt that recommendations related to medical applications have not been considered in detail, at any rate recently. A very creditable effort in collaboration between the various international organizations has therefore been undertaken, this series being sponsored jointly by the I.L.O., I.A.E.A. and W.H.O., with the latter organization taking responsibility for publication. It is certainly useful to have a *single* document to which reference can be made by those concerned with providing advice and recommendations in this field, and it is hoped that this trend can be continued.

This handbook, Volume 2 of the series, deals with the administration of *unsealed* radioactive materials to patients for radiotherapy, for nuclear medicine and for other clinical diagnostic applications. Different levels of radioactivity and different procedures are involved in radiotherapy and diagnostic studies. But it appears that in many centres these different functions may be undertaken within the same administrative unit, and department plans shown here allow for such facilities, including provision of some heavily shielded patient accommodation suitable for use with up to 450 mCi of ^{60}Co. Room plans for small, medium and large departments are provided, together with recommendations on appropriate facilities for clinicians, chemists, physicists and technicians in the preparation of radioactive materials and their use for both *in vivo* and some *in vitro* studies. These proposals can be useful in planning new departments, but should be adopted economically to correspond to real local requirements. Otherwise useful applications may be restricted by insistence on excessively expensive facilities for important but limited applications.

The recommendations intended for those responsible for providing Codes of Practice are fairly standard. But the various sections are well set out with sufficient overlap to ensure that each subject can be dealt with by the reader without detailed cross reference. Chapters deal with waste disposal, monitoring, decontamination, protection of patients, staff and the public together with accident procedures and first aid. Reduction of dose by choice of pharmaceutical and proper patient preparation is discussed. The chapter on "Equipment for Safe handling of Radioactive Materials" deals, rather surprisingly but usefully, with the measurement of γ emitters in well-type ion chambers, with the choice of collimators for scanning, and with the choice of pulse-height analysers for counting procedures. Under "Personnel Monitoring", great stress is laid on the usefulness of pocket-sized, acoustic warning devices to indicate to operators γ dose-rates in the range up to 100 mR/hour. Comprehensive appendices provide physical data for radioisotopes in common use, ranges of activity administered for various tests, and the doses to the corresponding critical organs.

Radiation protection officers will find this a useful addition to their book-shelves.

R. Oliver.

1976, *British Journal of Radiology*, *49*, 206–223

Review article

Craniopharyngioma: based on 160 cases*

By M. Banna, F.R.C.R., F.R.C.P. (C.), M.D. (Newcastle upon Tyne)†

(Received August, 1975)

ABSTRACT

This paper is the outcome of an extensive retrospective study of the clinical and radiological manifestations of a large number of craniopharyngiomas from five leading neuroscience centres in the U.K. The literature about this tumour has been reviewed with particular reference to its origin and radiological manifestations.

HISTORY AND ORIGIN OF THE TUMOUR

Many papers have been written about the clinical and surgical aspects of Rathke's pouch tumours, yet the man whose name is associated with the tumour has received little attention in the recent literature. According to the *Allgemeine Deutsche Biographie* (1888), Martin Heinrich Rathke was born on August 25, 1793 in Danzig on the Baltic Sea. He studied medicine in Göttingen, and qualified in Berlin in 1817. He practised general medicine in Danzig, and became the Chief Medical Officer of the town in 1825. He was appointed Professor of Physiology and Pathology in the University of Dorpat in 1829, and six years later he succeeded C. E. von Baer as Professor of Anatomy and Zoology in Königsberg University, a position which he held until he died on September 15, 1860. Rathke followed in the footsteps of von Baer, the founder of modern embryology, and it was during his study of the development of the pharynx that he discovered the origin of the pituitary gland. He wrote in 1838:

"For a long time, I have noted that early in the development of many mammals, long before the gum is formed, and at a point lying very posteriorly in the roof of the primitive mouth, under the developing skull base, there is a globular, somewhat irregular depression which looks like a thin-walled diverticulum. For many years I failed to discover its significance, as when I tried to pursue its growth by examining older embryos, I found that the diverticulum had disappeared. Finally I realized that it was to form the pituitary gland."

About 37 years later Mihalkivics (1875) established the stages of formation of the anterior lobe of the pituitary gland, and pointed out that the cells forming Rathke's vesicle multiply at different rates. Those in the anterior wall are the fastest to grow; they acquire a large mass and constitute the main bulk of the anterior lobe. Cells in the posterior wall remain very few in number and become the pars

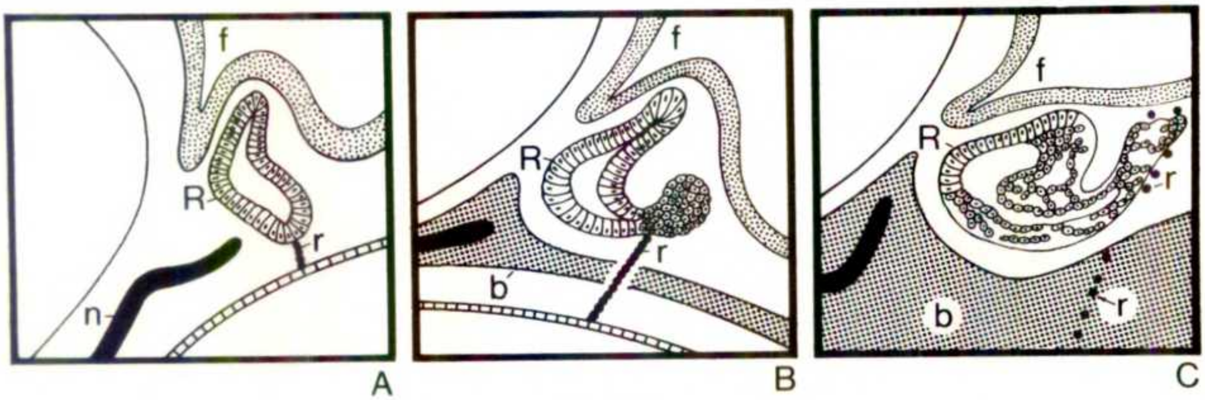

FIG. 1.

"Rotation" of the pituitary gland.

b = skull base, f = infundibulum, n = notochord, R = vesicle formed from Rathke's pouch, r = cell remnants of craniopharyngeal duct. Note how the site of these cells is changed as a result of "rotation" of the gland. In (A) they lie at the base of Rathke's sac, but some may later acquire a position above the rest of the gland (C).

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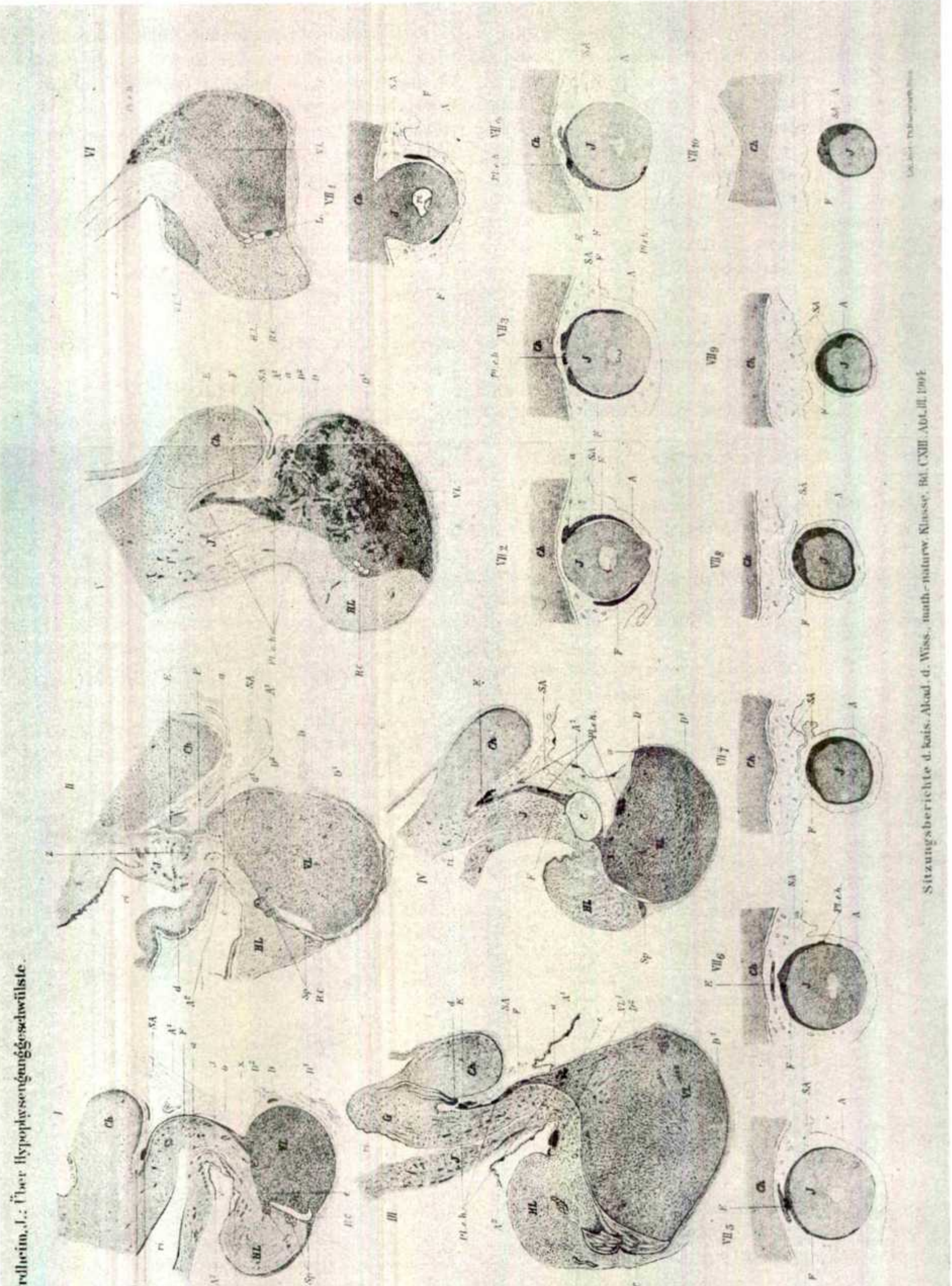
Erdheim, J.: Über Hypophysenganggeschwülste.
Sitzungsberichte d. kais. Akad. d. Wiss. math.-naturw. Klasse. Bd. CXIII. Abt. III. 1904.
I
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FIG. 2.

A copy of the original illustration by Erdheim showing the distribution of the squamous cell "islets" (Pl.e.h.) in different pituitary glands.

intermedia. The cavity of the vesicle is gradually reduced to a slit-like structure known as Rathke's cleft. It may persist into adult life as a distended cyst lined by cuboidal or columnar epithelium which is occasionally ciliated and may contain goblet cells. With the increase in size of Rathke's vesicle and perhaps because it is being compressed against the skull, the vesicle bends forward becoming crescentic and later U-shaped. As a result of this alteration in shape, sometimes described as "rotation" of the pituitary gland, the cells that were originally at the insertion of the craniopharyngeal duct are drawn away to the surface and acquire a new position above the rest of the gland (Fig. 1). This may explain why the majority of craniopharyngiomas occur above the pituitary fossa and only few are primarily intrasellar tumours.

The concept that craniopharyngioma arises from remnants of Rathke's pouch dates back to 1904 when Erdheim made an extensive study of squamous epithelial cells in the hypophyseal area which were vaguely described earlier by Luschka in 1860 and Saxer in 1902. Erdheim detected these cells only in glands that belonged to adult patients (Fig. 2). They were usually present in groups or "islets" of variable size and shape. They varied in number between different individuals but they were larger in elderly subjects, suggesting that they might have increased in size with advancing age. They were usually present along the anterior surface of the infundibulum of the pituitary gland and their structure was reminiscent of stratified squamous epithelium (Fig. 3). Some contained small cysts, but no hair follicles, sebaceous or sweat glands were found. Because of the similarity of these cysts to some pituitary tumours—unnamed at that time—Erdheim (1904) believed that both are of the same

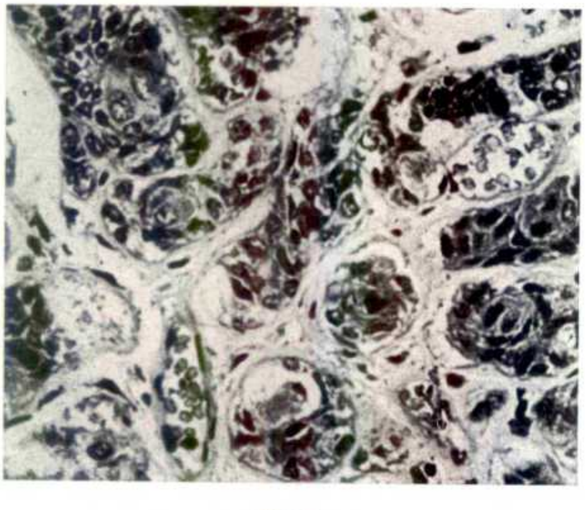


Fig. 3.

Squamous epithelial "islets" in the hypophyseal area.
Note the variability in size and shape of these islets and the presence of cystic degeneration in some of them. (By courtesy of Dr. A. F. J. Maloney, Edinburgh.)

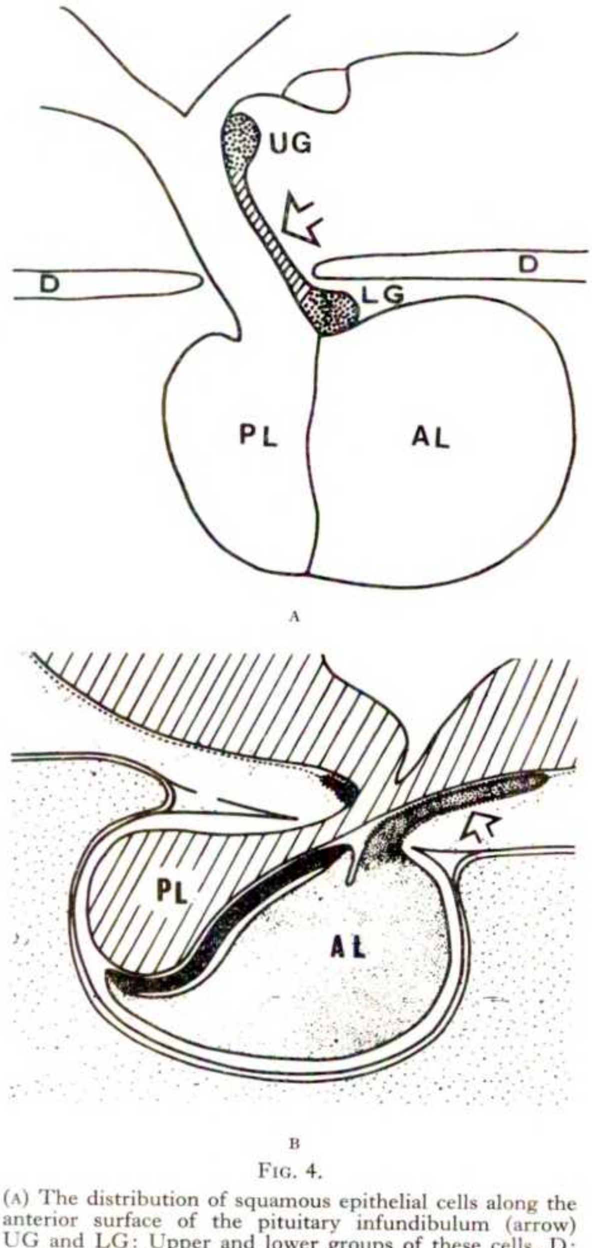


Fig. 4.

(A) The distribution of squamous epithelial cells along the anterior surface of the pituitary infundibulum (arrow) UG and LG: Upper and lower groups of these cells, D: diaphragma sellae, AL and PL: anterior and posterior lobes of pituitary gland.

(B) The position of the pars tuberalis (arrow), note its close similarity to the cells in A.

origin, and called this type of tumour *Hypophysenganggeschvülste* or hypophyseal duct neoplasm. He found in Mihalkivics publication a plausible explanation to the common location of these tumours above the sella.

Since Erdheim's contribution, few studies have been made of the squamous cells in the parapituitary area (Kiyono, 1924; Carmichael, 1931). These authors, unlike Erdheim, found cornification and keratohyalin in some squamous islets, and Susman (1932) found some squamous cells in children when he examined 230 pituitary glands.

The rarity of squamous cell rests in children led a number of investigators to challenge Erdheim's views that they give rise to tumours. Atwell (1926) described the developmental anatomy of the *pars tuberalis*, and suggested that at least some hypophyseal duct neoplasms were in fact tumours of the pars tuberalis (Fig. 4). Hunter (1955), while agreeing that these tumours were of squamous cell origin, produced histological evidence that these cells are formed by metaplasia from pituitary glandular cells, and believed that this was the reason why they were more frequently seen in adults. Notwithstanding these objections, the general concept is in favour of Erdheim's suggestion, but why Rathke's pouch tumours are more common in children despite the rarity of squamous cells in the pituitary area in the same age group, is not yet fully explained.

NOMENCLATURE

The name craniopharyngioma was introduced by Cushing in 1932. Commenting on the new terminology Cushing wrote:

"This admittedly somewhat cumbersome term has been employed, for want of something more brief to include the kalaidoscopic tumours, solid and cystic, which take their origin from epithelial

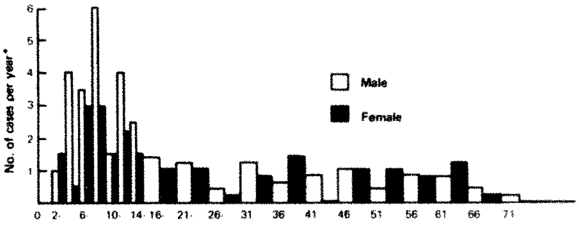


FIG. 5.

Incidence by age and sex in 160 cases.

TABLE I

THE INCIDENCE OF CRANIOPHARYNGIOMAS IN 1002 CASES COLLECTED FROM THE LITERATURE

Authors	No. of cases	Age in years							Sex	
		0–10	11–20	21–30	31–40	41–50	51–60	61–70	M	F
Bartlett, 1971	76	14	21	7	4	11	13	6		
Svolos, 1969	108	19	29	15	17	15	11	2	68	40
Matson and Crigler, 1969	57	39	18	—	—	—	—	—	—	—
Passerini and Vaghi, 1967	82	15	24	13	10	7	8	5	54	28
Rougerie and Fardeau, 1962	26	11	4	—	5	1	5	—	—	—
Krayenbuhl, 1961	59	13	14	7	8	12	4	1	34	25
Barnett, 1959	62	10	18	9	7	8	4	4	32	30
Northfield, 1957	49	11	12	10	3	10	3	—	26	23
Witt *et al.*, 1955	2	—	—	—	—	—	—	—	2	—
Iyer, 1952	1 (at birth)	—	—	—	—	—	—	—	—	—
Love and Marshall, 1950	100	19	34	12	15	11	8	1	56	44
Gordy *et al.*, 1949	51	17	12	5	8	6	2	1	27	24
Bayoumi, 1947	46	7	14	6	11	3	3	—	28	18
Globus and Gang, 1945	14	5	3	2	1	2	1	—	7	7
Wagener and Love, 1943	29	7	7	5	5	—	—	—	—	—
Bailey 1948	138	20	46	27	20	12	9	4	—	—
Cushing, 1932	92	14	29	19	13	9	6	2	—	—
Critchley and Ironside, 1926	19	1	8	5	2	1	2	—	10	9
Total number		223	293	142	129	108	79	28		

rests ascribable to an imperfect closure of the hypophyseal or craniopharyngeal duct. From a developmental stand-point, they are variously called hypophyseal-duct tumours, craniopharyngeal duct tumours and Rathke's pouch tumours; from an anatomical basis, interpeduncular or suprasellar cysts; and from a histopathological basis, adamantinomas, which is still more unfortunate."

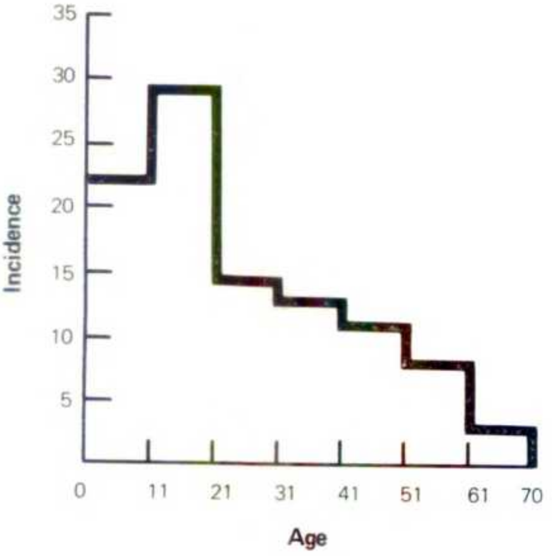


FIG. 6.

Incidence of craniopharyngiomas in 1,002 cases collected from the literature.

INCIDENCE

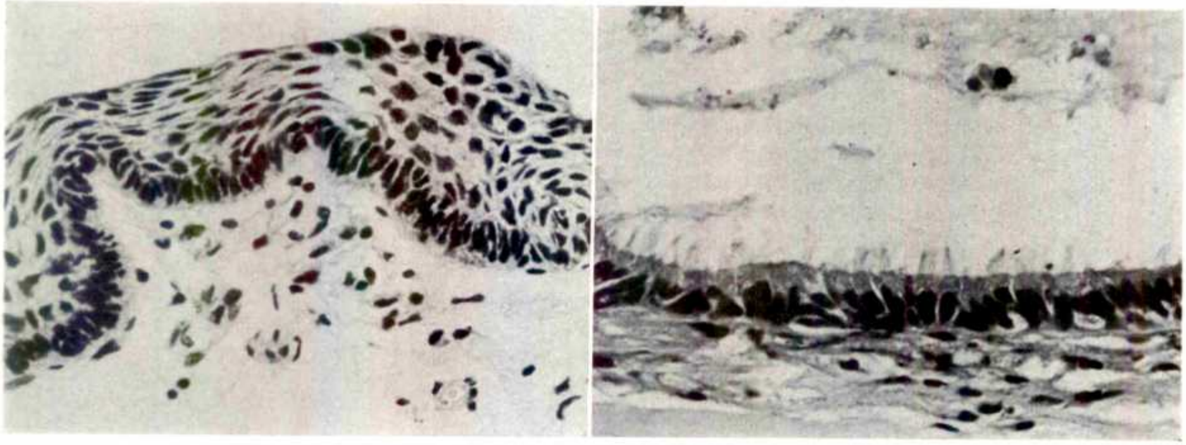
The incidence of craniopharyngioma among all brain tumours varies between 1·7 and 4·6 per cent (Zulch, 1965). In children, Ingraham and Scott (1946) estimated that these tumours form approximately 13 per cent of all intracranial neoplasms. In the general population there is probably one or two new cases per million per year.

AGE AND SEX

The youngest case ever reported was a neonate presenting with obstructive hydrocephalus (Iyer, 1952). In the present series, the youngest patients were between two and three years of age at the time of clinical presentation. In elderly patients the possibility of craniopharyngioma is often overlooked despite various reports to emphasize that an appreciable proportion of patients have their first symptom after the age of 40 (Russell and Pennybacker, 1961). In the present series 27 per cent of patients were over 40 years of age when they were first seen (Fig. 5). To assess the age distribution in a larger series, over 1,000 cases were collected from the literature (Table I). In these the incidence of the tumour was highest in the second decade and decreased with advancing age (Fig. 6).

PATHOLOGY

About 54 per cent of the tumours in the present series were cystic, 32 per cent were partly cystic and 14 per cent were solid. The cyst is usually multilocular, but occasionally the tumour is formed of a



A FIG. 7. B

Cystic craniopharyngioma.

(A) Stratified squamous epithelial lining of craniopharyngioma.

(B) Ciliated columnar epithelial lining from a cyst of Rathke's cleft.

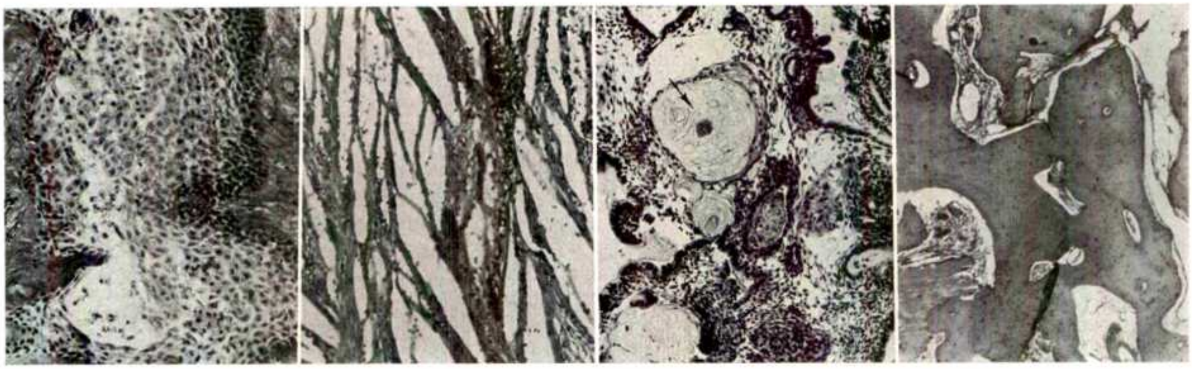


FIG. 8.

Solid craniopharyngioma.

(A) Adamantinomatous type: consisting of fibro-vascular cores surmounted first by a layer of dark staining columnar cells and then by more loosely packed squamoid cells.

(B) Cholesterol clefts.

(C) Epithelial whorls or "pearls".

(D) Bone formation.

single cyst. The inner wall may be smooth or may show papillary-like projections. The fluid within the cyst is yellow or brown in colour, and contains abundant glittering cholesterol material. It is often compared to "motor-oil" or "engine-oil", but when it contains dark brown blood the description "chocolate-oil" is applied. Rarely, the fluid is bright red as a result of recent haemorrhage. Although cholesterol is a characteristic constituent of the fluid within craniopharyngiomas, its concentration in one of the cases was only 0·07 per cent. The protein content within the same cyst was 6·5 mg per cent.

Approximately 96 per cent of all cystic craniopharyngiomas are lined by stratified squamous epithelium (Fig. 7). The remaining 4 per cent have an epithelial lining which is cuboidal or columnar. This is often ciliated and may contain goblet cells. The latter type of cyst is referred to as cyst of Rathke's cleft and is probably the same type of lesion once called colloid cyst of the pituitary gland.

The solid portion of craniopharyngioma (Fig. 8) consists of groups or trabecullae of epithelial cells supported by loose connective tissue in which myxomatous degeneration and cholesterol clefts may occur. The epithelium is formed of a basal columnar layer and then stratified squamous epithelium with some resemblance to the developing enamel cells (ameloblasts or adamantoblasts), hence it is sometimes described as the adamantinomatous type of craniopharyngioma. Other important features of craniopharyngioma include the presence of concentrically arranged cells undergoing coagulative necrosis and known as "epithelial pearls", calcification is common and bone formation may occur. There is no line of cleavage between the tumour and adjacent brain or pituitary tissue (Fig. 9), but reactive gliosis may occur and forcible removal is accompanied by severe damage to the hypothalamus. Thus, although the cellular structure of craniopharyngioma is that of a simple benign tumour, it is locally invasive and difficult to eradicate.

TABLE II

COMPARATIVE ANALYSIS OF THE MAIN RADIOLOGICAL FINDINGS IN CHILDREN AND ADULTS

	Children %	Adults %
Plain skull radiographs		
Normal	6	40
Abnormal	94	60
Tumour calcification	77·5	35
The sella		
Abnormal	70	50
Widened outlet	36	10
shortened or eroded dorsum	18	18
uniform expansion	13	17
destroyed	3	1

CLINICAL MANIFESTATIONS

The various manifestations of craniopharyngioma are well known and their incidence in the present series was reported elsewhere (Banna, 1973; Banna *et al.*, 1973).

TABLE III

INCIDENCE OF TUMOUR CALCIFICATION AND SELLA CHANGES AS REPORTED BY OTHER AUTHORS

Author	No. of cases	Calcification	Abnormal Sella	
Kanaka and Ramamurthi (1970)	58	children 71·5% adults 50%		
Matson and Crigler (1969)	57 children	almost 100%	approx. 50%	Also many showed separation of sutures
Svolos (1969) Olivercrone series	94 (out of 108)	53%	82·4%	
Passerini and Vaghi (1967)	82	56%	(a) With calcification <15 yrs: 88% >15 yrs: 86% (b) Without calcification <15 yrs: 100% >15 yrs: 73%	In the first decade calcification was present in 93%, the incidence gradually diminishing with advancing age Between 50–60 it was 12%
Rougerie and Fardeau (1962)	26	76%		
Barnett (1959)	62	73%		
Lindgren and Di Chiro (1951)	54	55%	87%	
Love and Marshall (1950)	100	56%	63%	
Gordy *et al.* (1949)	51	65%	63%	
McKenzie and Sosman (1924)	35	71%	76%	

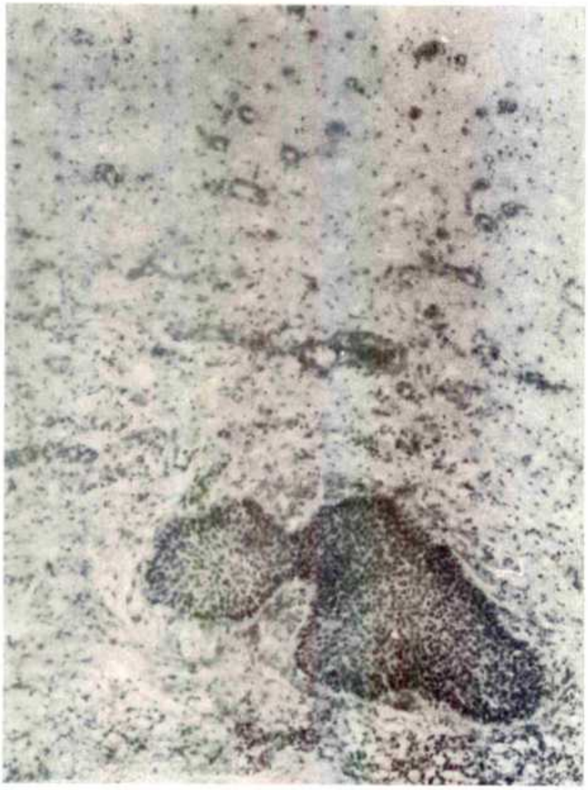


FIG. 9.

Boundary zone between craniopharyngioma and surrounding brain. Note absence of any line of cleavage.

RADIOLOGICAL MANIFESTATIONS

The pertinent radiological findings in children and adults are compared in Table II, and are compared with those published in the literature in Table III.

Various types of calcification may occur in craniopharyngioma (Fig. 10), usually involving the suprasellar region, but it may rarely be retrosellar or entirely within the sella (Fig. 11). It usually occurs about the mid-line but occasionally it may be limited to the peripheral part of a large lesion. In children, calcification in the sellar area is highly suggestive of craniopharyngioma, because in them other causes are rare. This is not the case in adults in whom tumours other than craniopharyngioma are more common. They include glioma, meningioma, cholesteatoma, ectopic pinealoma, pituitary adenoma, berry aneurysm and tuberculoma.

Regarding the "sellar changes", practically any type of sella may be seen in craniopharyngioma. On one hand, there are cases in which the sellar changes are classical of a suprasellar mass, but there are others in which they are indicative of an intrasellar neoplasm (Fig. 12). To exemplify the wide variation of the sellar changes, a few cases are illustrated in Fig. 13. Although advanced alteration or destruction of the sella is usually accompanied by a massive lesion, the reverse is not true. There were several cases in the series in which the sella was normal or showed minimal changes, yet the

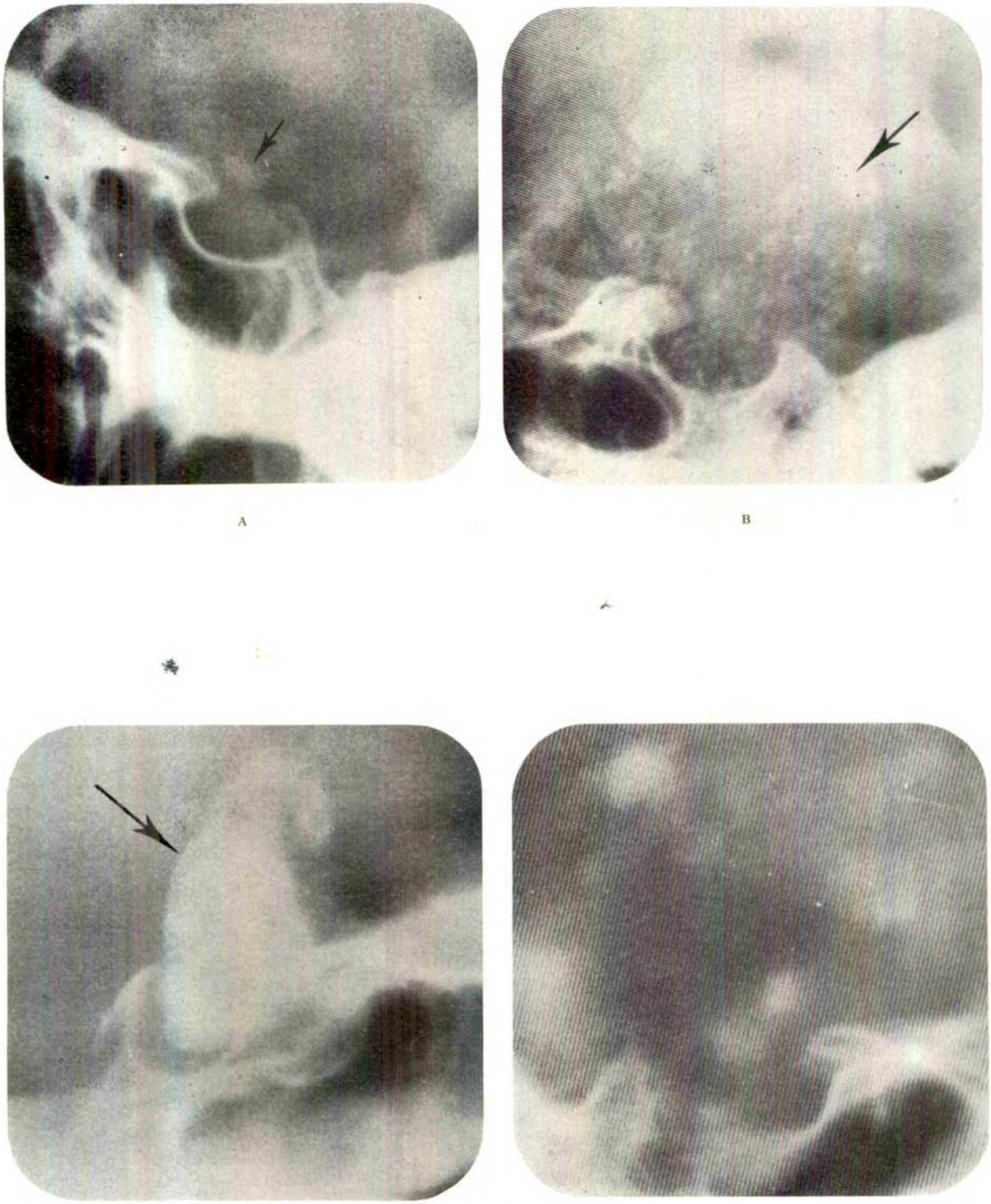
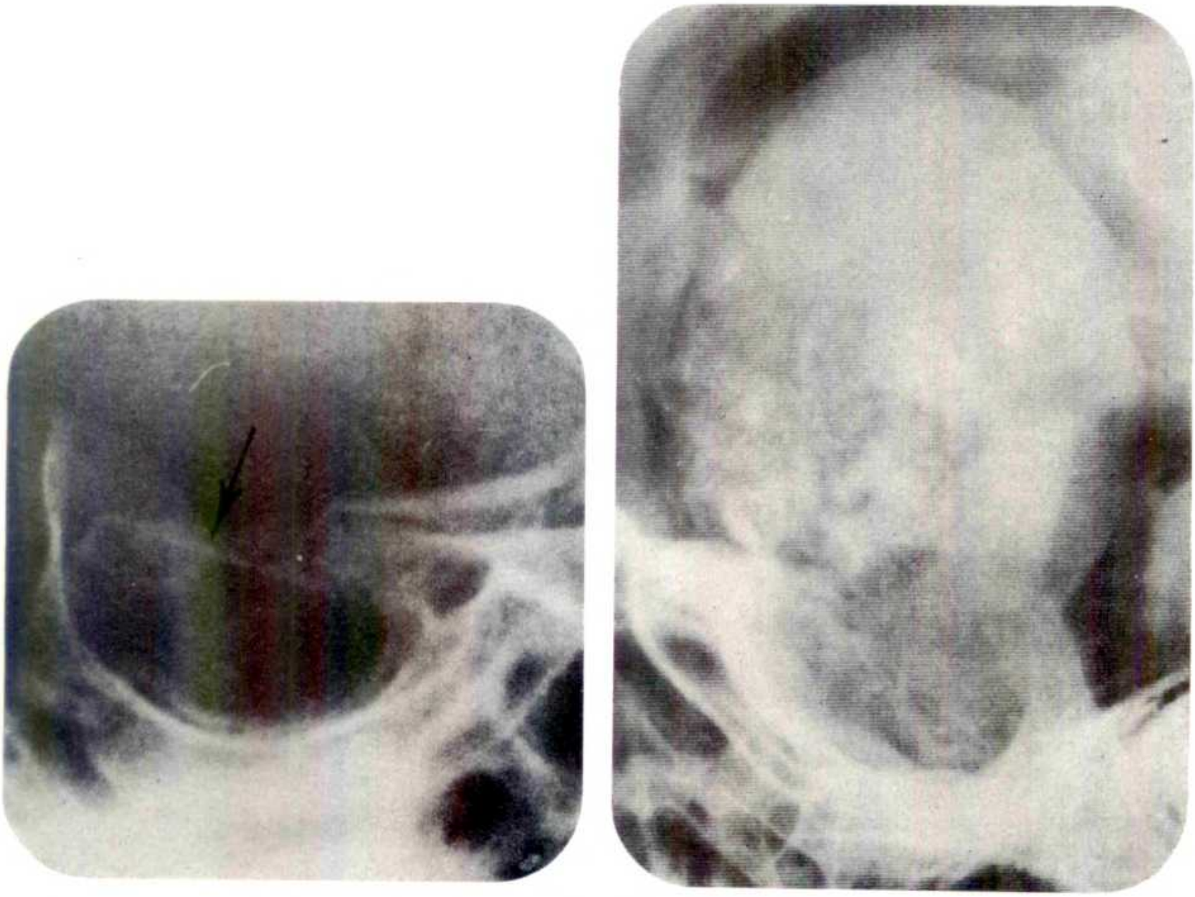


FIG .10.

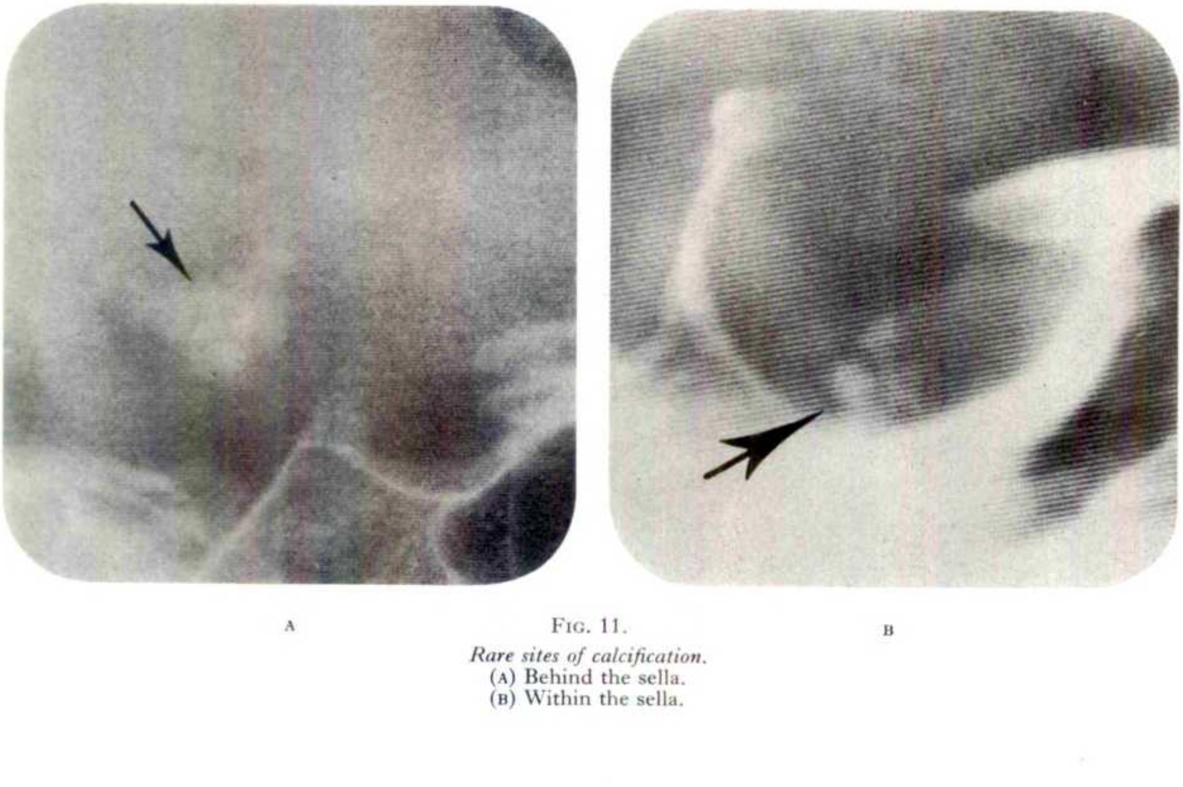
Types of calcification in craniopharyngioma.

(A) Single small calcified module. (B) Multiple nodular calcification. (C) Homogeneous dense calcification which histologically showed excessive bone formation. (D) Scattered ill-defined calcified nodules that mimic calcified tuberculomas.



E Fig. 10. F

(E) Curvilinear calcification. (F) Patchy calcification.



A Fig. 11. B

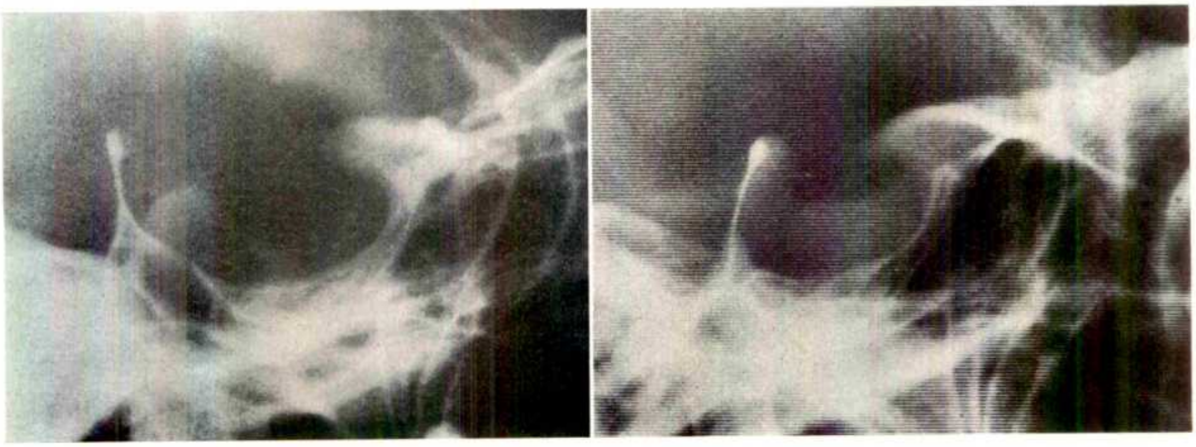
Rare sites of calcification.
(A) Behind the sella.
(B) Within the sella.

tumour size was enormous (Fig. 14) and might have been large enough to obstruct the interventricular foramen.

ANGIOGRAPHY

Conventional carotid angiography was performed in 56 adults and 19 children. Abnormal findings consistent with suprasellar tumours were found in 57 per cent of the patients in the first group and 74 per cent of the second. Attention should be drawn to the following points:

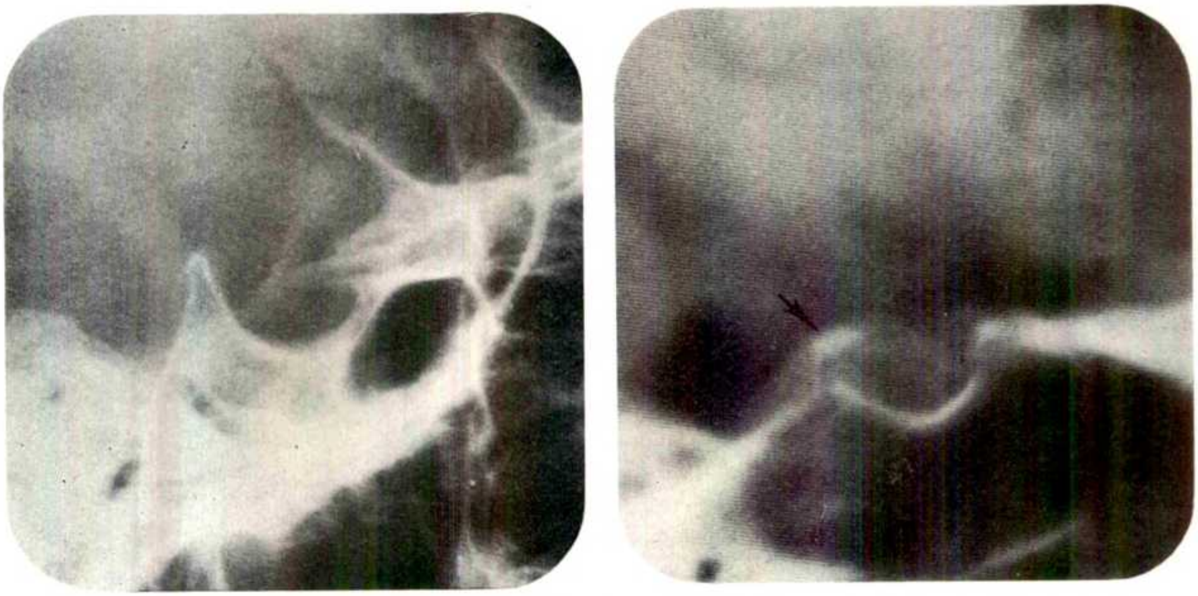
(1) When a pituitary or parapituitary tumour is suspected on clinical examination, the possibility of craniopharyngioma in an adult patient should not be eliminated on the basis of normal skull radiographs and a normal carotid angiogram. The present study showed that approximately two-fifths of the patients in the adult age groups had



A FIG. 12. B

(A) Widening of the outlet of the sella in keeping with a suprasellar tumour.

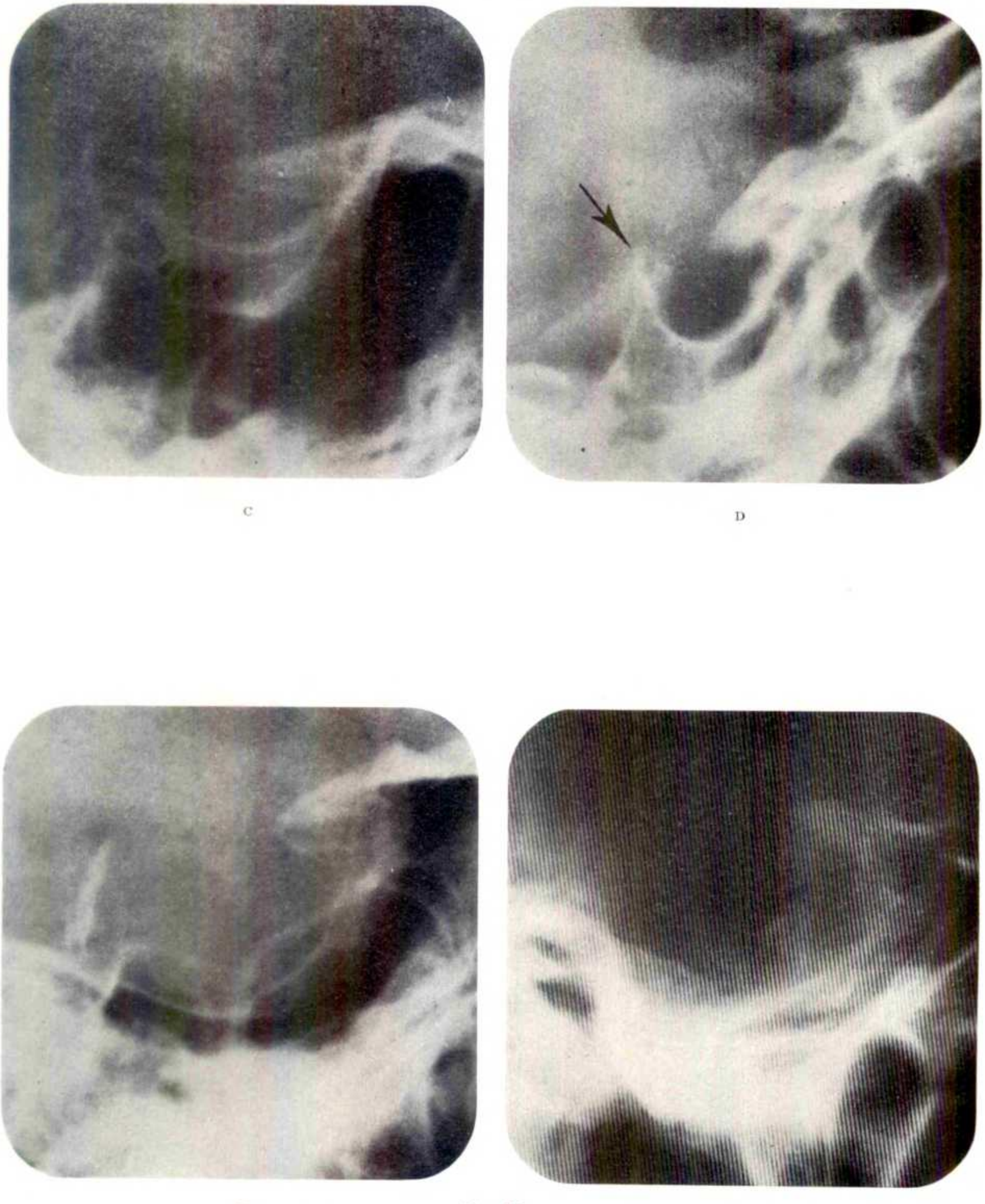
(B) Uniform expansion of the sella indicative of an intrasellar lesion.



A FIG. 13. B

Variation of sella changes in craniopharyngioma.

(A) Backward tilt of the dorsum sellae. (B) forward tilt of the dorsum.



C

D

E

F

Fig. 13.

Variation of sella changes in craniopharyngioma.

(C) Double outline of the floor of the sella. (D) J-shaped sells. (E) Ballooned sella. (F) Complete destruction of all sella components. Note that with the exception of minute flecks of calcium in (D) (arrow) all these examples and the preceding ones were not associated with tumour calcification.

normal skull radiographs and normal carotid angiograms. This is not the case in children in whom some abnormality was detected on the plain skull radiographs in 94 per cent of the cases.

(2) In more than 50 per cent of the angiograms there was no elevation of the horizontal segment of the anterior cerebral artery, although in some the tumour extended high enough to obstruct the foramen of Monro. One assumes that in such a case the tumour grows like a pear behind the anterior portion of the circle of Willis.

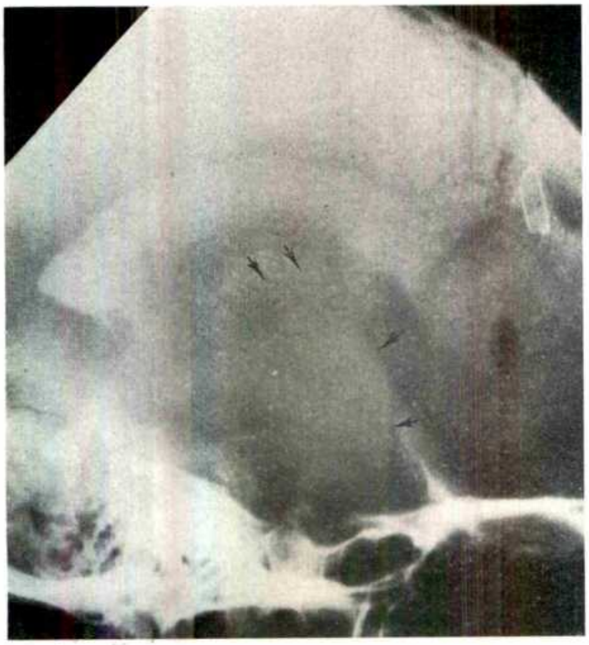
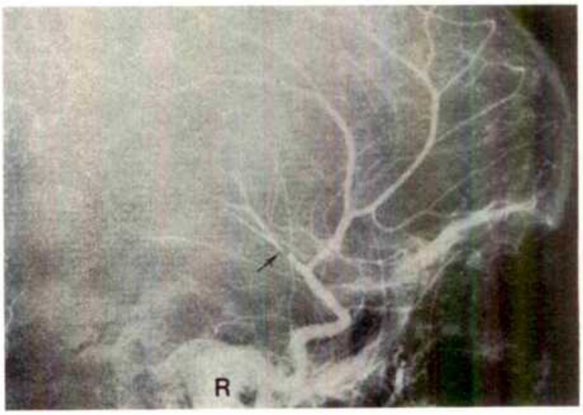


FIG. 14.

Conray ventriculogram of a massive craniopharyngioma occupying a large part of the 3rd ventricle (arrows) and displacing the aqueduct and 4th ventricle yet there are only minimal changes in the sella in the form of slight erosion of the dorsum sellae.



A

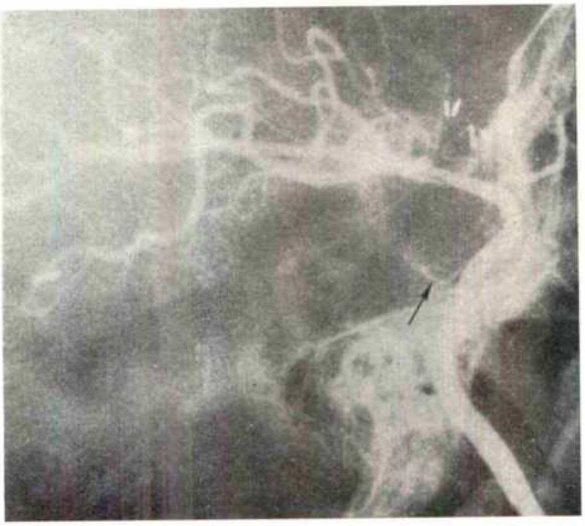
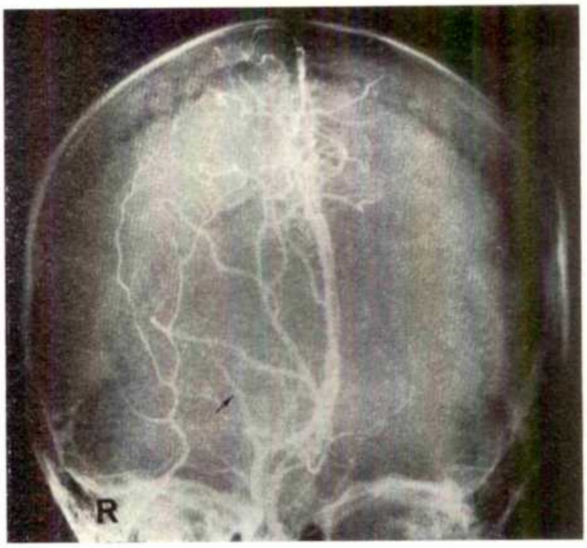


FIG. 15.

Selective internal carotid injection illustrating enlargement of the meningohypophyseal artery (arrow) as a rare finding in craniopharyngioma.



B

FIG. 16.

(A) lateral and (B) anterio-posterior views of a right common carotid angiogram of an eight year old boy presenting with sudden collapse who was found to have a craniopharyngioma extending into the temporal lobe and occluding the middle cerebral artery (arrow).

(3) There were cases in the series which showed almost identical filling defects in the 3rd ventricle, yet the horizontal segment of the anterior cerebral artery might be elevated in one and not the other. Gado and Bull (1973) explained that an artery which follows a straight horizontal direction is more amenable to displacement than that running forward and medially.

(4) No pathological tumour circulation was noted in any of the cases, but the meningo-hypophyseal artery was enlarged in one case (Fig. 15).

(5) Vascular occlusion in a fashion similar to that seen occasionally in parasellar meningioma was seen in one case. This was a child investigated for sudden collapse and was found to have occlusion of the middle cerebral artery from a craniopharyngioma extending into the middle cranial fossa (Fig. 16).

(6) Vertebral angiography reveals the posterior extension of craniopharyngioma (Fig. 17) and its indication ought to be considered if "total" removal of the tumour is contemplated.

AIR STUDIES

The results of analysis of the pneumoencephalograms seemed to agree with the concept that there are two distinct sites of origin of craniopharyngioma; one above the diaphragma sellae and the other below it (Fig. 18). The first obliterates the suprasellar cistern at an early stage and is invariably associated with a filling defect in the 3rd ventricle (Fig. 19).

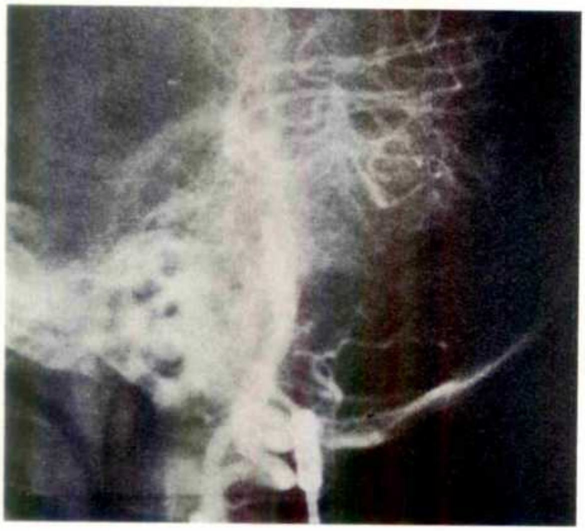
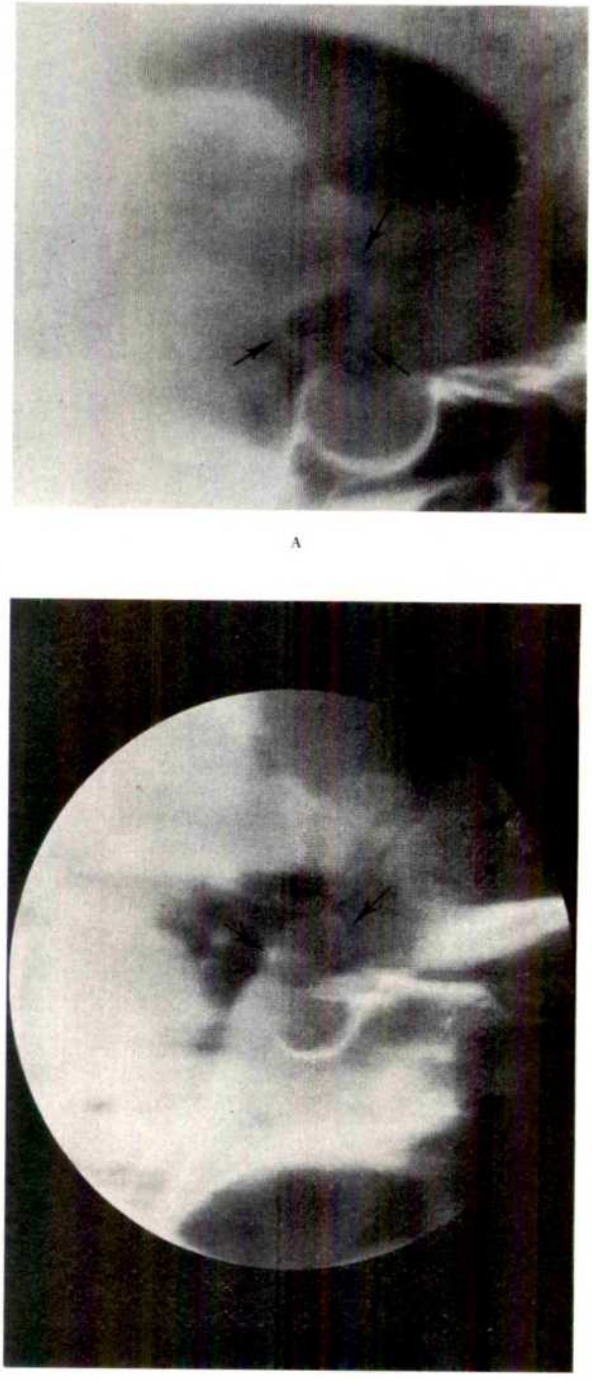


Fig. 17.

Posterior displacement of the basilar artery by craniopharyngioma. Performed after ventriculo-atrial shunting.



A

B

Fig. 18.

Pneumoencephalograms.

(A) Craniopharyngioma that appears to arise above the diaphragma sellae (arrows).

(B) Craniopharyngioma that appears to arise from within the sella and its extension above the sella (arrows) is elevating the suprasellar cistern.

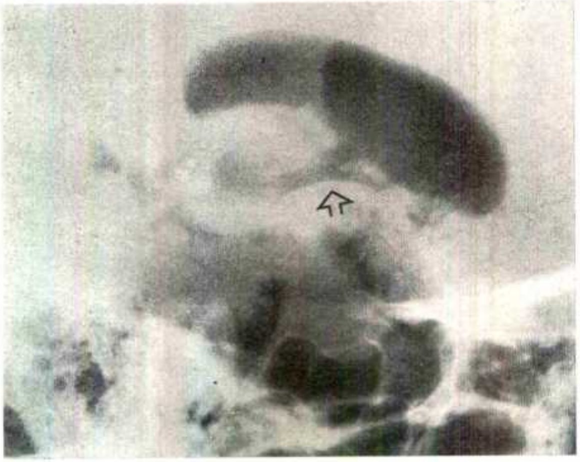


FIG. 19.
Pneumoencephalogram: filling defect in the 3rd ventricle from craniopharyngioma (arrow).

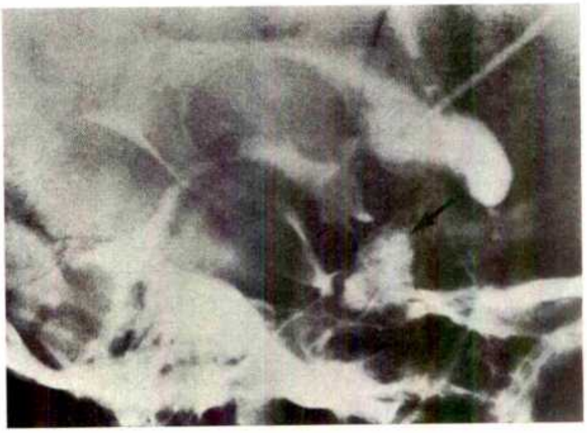


FIG. 20.
Conray ventriculogram: calcified craniopharyngioma (arrow) growing upwards and slightly forwards leaving the anterior recesses of the 3rd ventricle intact.

The sella may show widening of the antero-posterior diameter or it may remain intact. Whether obliteration of the cistern is due to tumour invasion or to its compression against the diaphragma sellae is not clear, but there was no case in the series in which the cistern was outlined beneath a craniopharyngioma. In the second type where the tumour was thought to originate below the diaphragma sellae (approximately 15 per cent of cases in the series), the sellar changes were consistent with intrasellar tumour, and were often difficult to differentiate from those caused by pituitary adenoma. If the lesion was small the suprasellar cistern was outlined above the tumour and the anterior recesses of the 3rd ventricle were not necessarily deformed. In some cases the tumour extended in front of the 3rd ventricle leaving the anterior recesses intact (Fig. 20); depending on the relationship of the recesses to the pituitary fossa.

In any age group, tumour growth in various directions was seen but massive lesions were more frequent in children and often appeared to arise above the sella (Fig. 21).

CYSTOGRAPHY

The inside lining of a cystic craniopharyngioma can be outlined by air or steripaque (Fig. 22). The use of thorium is long out-dated. Steripaque is an inert substance composed of very fine barium particles ranging from 0·1 to 0·5 μ in size. It is usually injected undiluted in a dose of 1–3 cm^3. It readily adheres to the cyst wall, and remains there indefinitely. Its value is to assess the size of the tumour by comparing sequential radiographs taken in the brow-up and brow-down positions.

ISOTOPE SCINTIGRAPHY

Only the large and solid craniopharyngioma can be detected by isotope scanning (Fig. 23). Small tumours and cystic lesions do not appear on the isotope scan.

COMPUTERIZED TOMOGRAPHY

With this technique, the cholesterol content of the tumour has negative values on the computer print-out and appears as an area of very low density on the Polaroid picture (Ambrose, 1973). Following contrast enhancement, the "capsule" of the tumour may appear very dense. These features are extremely helpful and are almost pathognomonic of cystic craniopharyngioma. The solid non-calcified craniopharyngioma, on the other hand, appears as an infiltrative lesion and is impossible to differentiate from invasive tumours in the hypothalamus. As in any other pituitary tumour, it is only the suprasellar extension of the lesion that can be detected by computer tomography (Fig. 24).

ACKNOWLEDGMENTS

The material forming the basis of the present paper was collected from the Institute of Neurology (Queen Square, London) by permission from Dr. J. W. Bull; the Institute of Neurological Sciences (Glasgow) by permission from Dr. J. L. Steven; the Regional Neurological Centre (Newcastle upon Tyne) by permission from Dr. G. L. Gryspeerdt

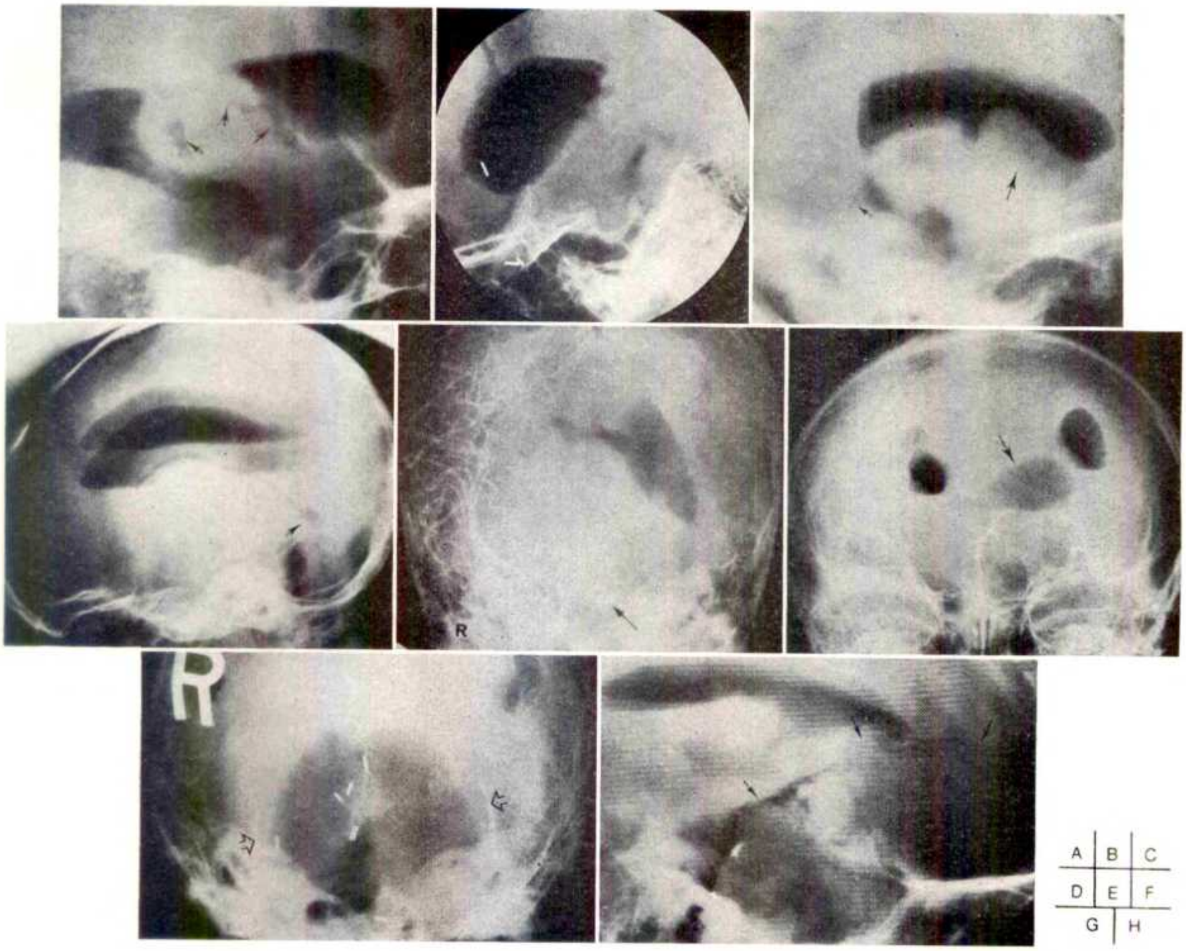


Fig. 21.

Tumour extension in various directions.

(A) Upward extension into the 3rd ventricle (arrows) in a fashion that simulates a primary intraventricular neoplasm.

(B) Occlusion of the foramen of Monro. Note relatively little change in the sella.

(C) Tumour extension into the frontal lobes. Note despite the large tumour volume (arrows) there is little change in the sella.

(D) Tumour extension into the brain stem and posterior fossa. Arrow points at the displaced 4th ventricle. Note also the posterior displacement of the pontine cistern.

(E) Extension into one cerebral hemisphere. The illustration is a combined air ventriculogram and right carotid angiogram showing displacement of the ventricular system to the left. There was no filling of the anterior cerebral artery from that side. Arrow points to an area of faint calcification.

(F) Tumour extension between the two cerebral hemispheres. Arrow points to an air-filled cyst between the two lateral ventricles.

(G) Excavation of the pituitary fossa. This air-filled mid-line cyst represents only the intrasellar portion of a massive craniopharyngioma. Arrows point to what probably were the anterior clinoid processes. The extrasellar portion of the tumour is shown in (H). This patient was alive and reasonably well 15 years after these radiographs were taken.

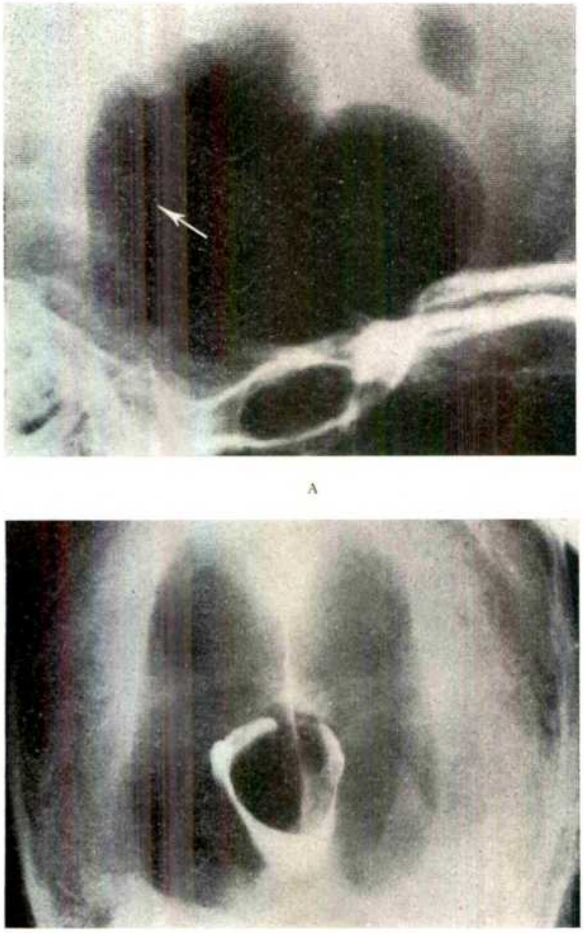


FIG. 22.

Cystography.

(A) Using air as a contrast medium: arrow points to papillary outgrowths within the cyst.

(B) Using steripaque: the solid part of the tumour was well outlined in the Towne's projection.

and from the Hospital for Sick Children and the Neurosurgical Unit of Guy's, Maudsley and King's College Hospitals by permission from Dr. R. D. Hoare. The photographic illustrations were carried out by the photographic department of Newcastle-upon-Tyne University, and the study was supported by a grant from the research committee of the same University.

REFERENCES

Allgemeine Deutsche Biographie, 1888. Vol. 27, pp. 352–355 (Verlag von Duncker and Humblot, Leipzig).

AMBROSE J., 1973. Computerized transverse axial scanning (tomography). Part 2. Clinical application. *British Journal of Radiology*, *46*, 1023–1047.

ATWELL, W. J., 1926. The development of the hypophysis cerebri in man, with special reference to the pars tuberalis. *The American Journal of Anatomy*, *37*, 159–179.

BANNA, M., 1973. Craniopharyngioma in adults. *Surgical Neurology*, *1*, 202–204.

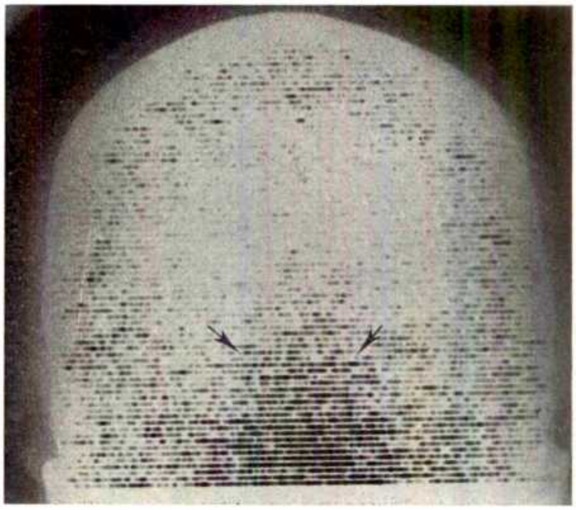


FIG. 23.

Isotope scintigraphy.

Using ^{99}Tc^{m} the solid part of craniopharyngioma (arrows) was outlined. Further examinations showed that the tumour was larger than what is here shown.

BANNA, M., HOARSE, R. D., STANLEY, P., and TILL, K., 1973 Craniopharyngioma in children. *The Journal of Pediatrics*, *83*, 781–785.

BAILEY, P., 1948. In *Intracranial tumours*, 2nd edn., pp. 113–137 (Charles C. Thomas, Springfield, Illinois, U.S.A.).

BARNETT, D. J., 1959. Radiologic aspects of craniopharyngiomas. *Radiology*, *72*, 14–18.

BARTLETT, J. R., 1971. Craniopharyngiomas. An analysis of some aspects of symptomatology, radiology and histology. *Brain*, *94*, 725–732.

BAYOUMI, M. L., 1947. Pathological study of pituitary tumours especially as regards the types, incidence and course. (M.D. Thesis, Edinburgh University.)

CARMICHAEL, H. T., 1931. Squamous epithelial rests in the hypophysis cerebri. *Archives of Neurology and Psychiatry*, *26*, 966–975.

CRITCHLEY, M., and IRONSIDE, R. N., 1926. The pituitary adamantinomata. *Brain*, *49*, 437–481.

CUSHING, H., 1932. The craniopharyngiomas. In *Intracranial Tumours*, pp. 93–98. (Bailliere, Tindall and Cox, London.)

ERDHEIM, J., 1904. Über Hypophysenganggeschwülste und Hirncholesteatome. Sitzungsberichte der Mathematisch. *Naturwissenschaftlichen Klasse der Kaiserlichen Akademie der Wissenschaften 113, Abteilung LLL*, 537–726.

GADO, M., and BULL, J. W. D., 1971. The carotid angiogram in suprasellar masses. *Neuroradiology*, *2*, 136–153.

GLOBUS, J. H., and GANG, K. M., 1945. Craniopharyngioma and suprasellar adamantinoma. *Journal of the Mount Sinai Hospital*, *46*, 221–276.

GORDY, P. D., PEET, M. M., and KAHN, E. A., 1949. The surgery of the craniopharyngioma. *Journal of Neurosurgery*, *6*, 503–517.

HUNTER, I. J., 1955. Squamous metaplasia of cells of the anterior pituitary gland. *Journal of Pathology and Bacteriology*, *69*, 141–145.

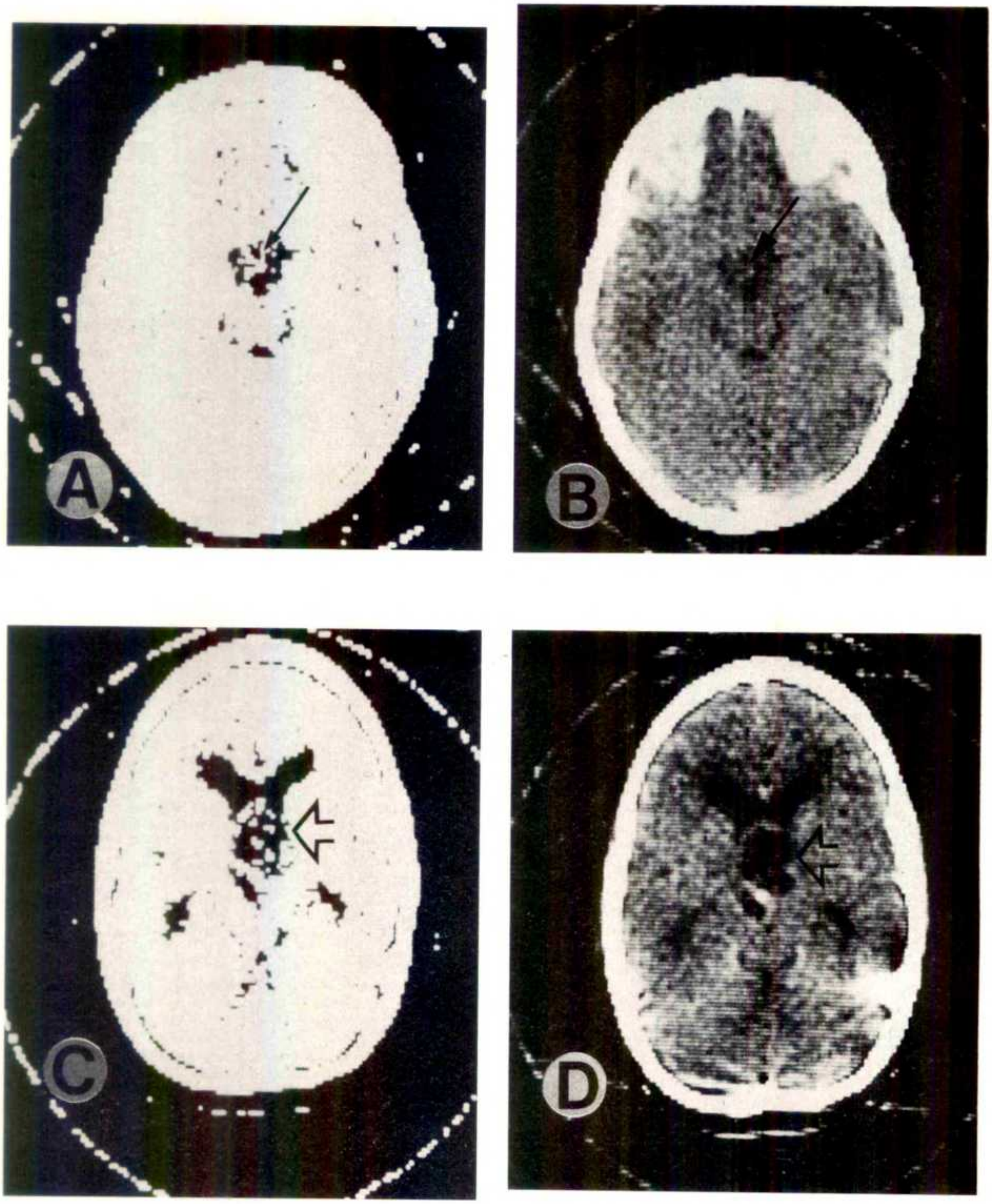


Fig. 24.

(A and B) Show a small suprasellar extension into the chiasmatic cistern (arrows). (A) measured at window level 6, (B) is contrast enhanced.

(C and D) Suprasellar cystic craniopharyngioma (arrows). (C) measured at window level 4, (D) is contrast enhanced.

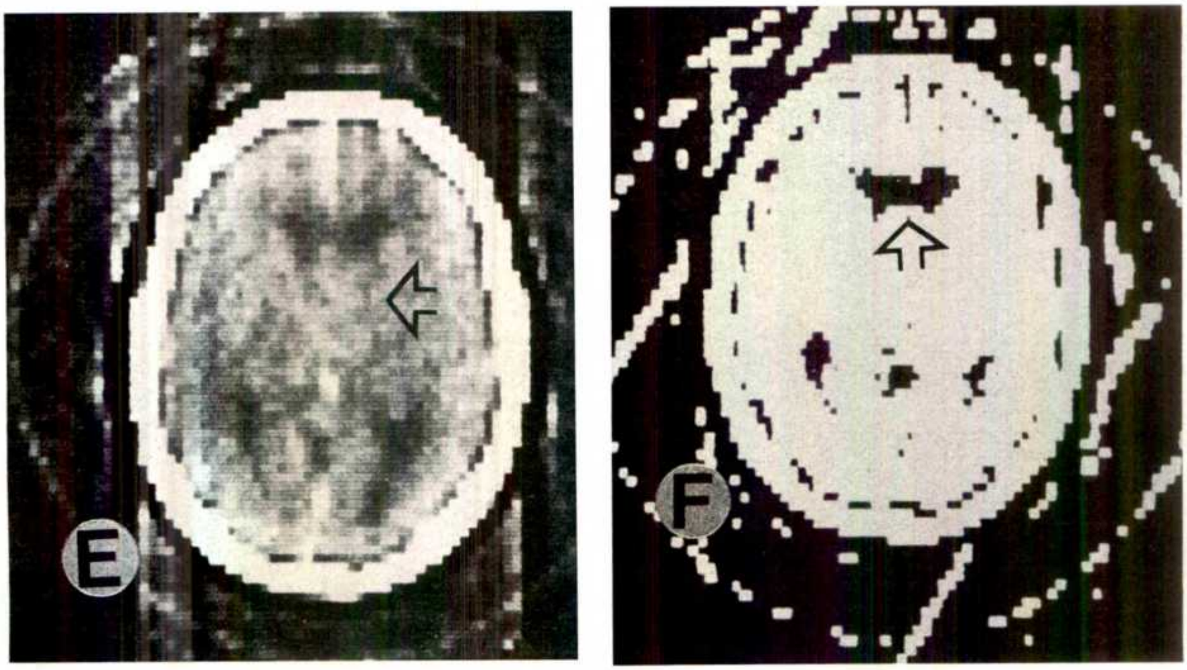


FIG. 24.

(E and F) Suprasellar non-calcified solid craniopharyngioma. (E) measured at window level 10. (F) is contrast enhanced.

INGRAHAM, F. D., and SCOTT, H. W., 1946. Craniopharyngioma in children. *Journal of Pediatrics*, *29*, 95–116.

IYER, C. G. S., 1952. Case report of an adamantinoma present at birth. *Journal of Neurosurgery*, *9*, 221–228.

KANAKA, T. S., and RAMAMURTHI, 1970. Craniopharyngiomas. *Neurology India*, *18*, 75–78.

KIYONO, H., 1924. Uber des Vorkommen von Plattenepithherden in der Hypophyse. *Virchows Archiv. für Pathologische Anatomie und Physiologie*, *252*, 118–145.

KRAYENBUHL, H., 1961. Hypophyseal adenomas and craniopharyngiomas. *Excerpta Medica* (*International Congress Series*), No. 36, E.10.

LINDGREN, E., and DI CHIRO, G., 1951. Suprasellar tumours with calcification. *Acta Radiologica*, *36*, 173–195.

LOVE, J. G., and MARSHALL, T. M., 1950. Craniopharyngiomas. *Surgery, Gynecology and Obstetrics*, *90*, 591–601.

MCKENZIE, K. G., and SOSMAN, M. C., 1924. The roentgenological diagnosis of craniopharyngeal pouch tumours. *American Journal of Roentgenology*, *11*, 171–176.

MATSON, D. D., and CRIGLER, jun., J. F., 1969. Management of craniopharyngioma in childhood. *Journal of Neurosurgery*, *30*, 377–390.

MIHALKIVICS, V., 1875. Wirbelsaite und Hirnanhang. *Archives für Mikroskopische Anatomie*, *11*, 388–441.

NORTHFIELD, D. W. C., 1957. Rathke-pouch tumours. *Brain 80*, 293–312.

PASSERINI, A., and VAGHI, M. A., 1967. II Craniopharyngioma: studio radiologico Di 82 Casi. *Nuntius Radiologicus*, *Vol. 33*, *No. 7*, 851–871.

ROUGERIE, J., and FARDEAU, M., 1962. *Les cranio-pharyngiomes*. (Masson et Cie).

RUSSELL, R. W. R., and PENNYBACKER, J. B., 1961. Craniopharyngioma in the elderly. *Journal of Neurology, Neurosurgery and Psychiatry*, *41*, 1–13.

SUSMAN, W., 1932. Embryonic epithelial rests in the pituitary. *British Journal of Surgery*, *19*, 571–576.

SVOLOS, D. G., 1969. Craniopharyngiomas. A study based on 108 varified cases. *Acta Chirurgica Scandinavica Supplement*, *403*, 7–44.

WAGENER, H. P., and LOVE, J. G., 1943. Fields of vision in cases of tumour of Rathke's pouch. *Archives of Ophthalmology*, *29*, 873–887.

WITT, J. A., MACCARTY, C. S., and KEATING, jun., F. R., 1955. Craniopharyngioma (pituitary adamantinoma) in patients more than 60 years of age. *Journal of Neurosurgery*, *12*, 354–360.

ZÜLCH, K. J., 1965. *Brain Tumours. Their biology and Pathology*, pp. 62–68, (Springler, New York).

1976, *British Journal of Radiology*, *49*, 224–232

Late effects of X irradiation in patients treated for metropathia haemorrhagica

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(*Received October, 1975*)

ABSTRACT

We have previously reported on the causes of death among 2,068 patients treated with X irradiation for metropathia haemorrhagica at three Scottish radiotherapy centres between 1940 and 1960 (Doll and Smith, 1968). This cohort of women has now been followed up for a further seven years. 500 (24 per cent) women have now died, 78 (3·8 per cent) have emigrated and 25 (1·2 per cent) could not be traced.

The numbers of deaths from different causes have been compared with the numbers expected in a population of similar age and sex exposed to the Scottish national mortality rates over the same period. An excess of deaths from leukaemia (seven observed, 2·3 expected) and of cancers of the heavily irradiated sites (59 observed, 40·1 expected) continues to be observed five or more years after treatment. There is no indication of any change in the excess death rate, due to cancers of sites in the radiation field, with time since treatment up to at least 20 years after the radiation exposure. Over the same period the number of deaths from cancer of the breast was below expectation (ten observed, 22·3 expected) and no increased mortality from coronary disease was seen (102 observed, 100·9 expected).

The mean dose of radiation to the bone marrow has been determined for each woman and it is estimated that the excess rate of leukaemia in the first 20 years after treatment is about 1·1 per million women per year per rad. This figure is in accord with the estimates derived from the survivors of the atomic bomb explosions in Hiroshima and Nagasaki and among patients with ankylosing spondylitis treated with X irradiation. However, the finding of no excess risk of leukaemia among women treated with radiation for cancer of the cervix (Hutchison, 1968) suggests that the simple assumption of a linear dose-response relationship for leukaemia is incorrect, at least when high doses of radiation are delivered to a small volume of marrow.

We have previously reported the results of a follow-up study of 2,068 women treated for metropathia haemorrhagica by X irradiation of the ovaries at three Scottish radiotherapy centres between 1940 and 1960 (Doll and Smith, 1968). The mortality experience of the women up to January 1, 1964 was compared with the national mortality rates for Scotland. Five or more years after treatment, an excess mortality rate was noted for leukaemia and for cancers of sites included in the treatment radiation field, while there was a deficit of deaths from cancer of the breast. The numbers of deaths from coronary thrombosis and from all other causes were close to those expected.

At the time of this study the women had been followed for between three and 24 years, with a mean of 13·6 years. We have since extended the period of follow-up of this population in order to examine in more detail the late effects of the radiation exposure; and, in particular, to assess whether there has been any change in the risk of dying from a radiation associated cancer with time since the initial exposure.

THE DATA

Details of the study population and the nature of the radiation exposure have been described previously (Doll and Smith, 1968). All of the women were treated with X rays for metropathia haemorrhagica (97 per cent) or other benign gynaecological conditions (3 per cent) between 1940 and 1960. For much of this period X irradiation was used in preference to surgery or hormone therapy for the treatment of metropathia haemorrhagica in the three selected centres and there was no selection of the more seriously ill patients for radiotherapy.

An attempt has now been made to extend the follow-up from January 1, 1964, when the last study was completed, as follows: Aberdeen to January 1, 1971; Edinburgh to January 1, 1972 and Dundee to January 1, 1973. The results of this follow-up are shown in Table I. The different dates for each centre reflect the order in which the follow-up of patients from each of the centres was undertaken. At the time of follow-up 2,040 (98·7 per cent) women had been treated only once; but 24 (1·2 per cent) had been irradiated a second time and three (0·1 per cent) a third time for recurrence of bleeding. In some cases subsequent therapy was with radium. Eighty-five women were found to have received further therapeutic irradiation for other reasons—74 (3·5 per cent) for the treatment of a subsequent cancer and 11 (0·5 per cent) for thyrotoxicosis or some other benign condition. The period of follow-up ranges from 10–31 years with a mean of 19·0 years. Seventy-one per cent of the patients were still alive, 4 per cent had emigrated, 24 per cent had died and 1·2 per cent (25) were incompletely traced. Copies of the death certificates were obtained for all those who had died and the causes of death were

TABLE I

STATE OF PATIENTS AT END OF PERIOD OF FOLLOW-UP

	Radiotherapy centre			Total	
	Aberdeen	Edinburgh	Dundee		
	Date of follow-up				
State	1.1.1971	1.1.1972	1.1.1973	No.	%
Alive	248	514	702	1,464	70·8
Dead	66	282	152	500	24·2
Emigrated	9	42	27	78	3·8
Lost	1	11	13	25	1·2
Total	324	849	894	2,067*	100·0

*2,068 patients were included in the previous report (Doll and Smith, 1968). One patient was found to have been incorrectly included twice, another was found to have received radium in her first treatment course and has therefore been excluded and one patient is now included whose notes were first found after 1968.

classified according to the seventh revision of the International Classification of Disease[†] (World Health Organization, 1957).

The numbers of deaths expected were estimated by multiplying the number of woman-years at risk during the period of the study by the corresponding national mortality rates for Scotland. The numbers of years at risk were calculated separately for each five-year age group and for each quinquenium from 1941–45 to 1966–70 and for the two-year period 1971–72. Women were regarded as having left the study on the date of death or emigration or on the last date traced, if this preceded the follow-up date appropriate for the centre. Age-specific death rates for the general population for the corresponding periods were calculated from the data published annually by the Registrar General for Scotland, and the years at risk in each age and period group were multiplied by these rates to give the numbers of deaths expected by cause.

RESULTS

Five hundred women are known to have died in the period between first treatment and the last follow-up. The distribution of these deaths by selected causes is shown in Table II together with the expected mortality. The number of deaths from all causes is remarkably close to that expected and there is only a slight, not statistically significant, excess of deaths attributable to all neoplasms. As previously reported, however, there is a significant ($P<0{\cdot}03$) excess of deaths from leukaemia, seven observed and only 2·7 expected, one more death from this cause having occurred since the 1964 follow-up. There is also a significant increase in mortality from cancer of the heavily irradiated sites and a marked deficit of deaths from cancer of the breast. The increased mortality due to multiple myeloma or the lymphomas is not statistically significant. The numbers of deaths from other causes are close to those expected, except for two deaths from aplastic anaemia and three from non-neoplastic diseases of the female genitals.

We have discussed previously (Doll and Smith, 1968) how the initial pelvic examination, to which all the women in the study will have been subjected, may have selected out those women with existing primary pelvic cancers and thus a deficit of deaths from such causes might be expected in the period immediately following the initial treatment. We have therefore compared the observed and expected deaths for different periods after the initial treatment and these results are shown in Table III. The excess of deaths from leukaemia and from cancers in the heavily irradiated sites occurred only five years after irradiation. An excess is still apparent, though not statistically significant, 20 years or more following treatment among cancers of the heavily irradiated sites. The deficiency of deaths due to cancer of the

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[†] In our 1968 paper, deaths were tabulated as due to coronary disease if they would have been given the code 420 under the seventh revision of the International Classification of Deaths (World Health Organization, 1957). However, the coding for coronary disease was extensively revised at the eighth revision (World Health Organization, 1967) and in this paper we have tabulated deaths coded 420 and 422·1 (seventh revision) as coronary disease; these codes are approximately equivalent in the eighth revision to the codes 410·0, 410·9, 411·0, 411·9, 412·9, 413·0, 413·9, and approximately half of deaths coded as 412·0.

TABLE II

Numbers of deaths observed and expected, by cause

Cause of death (I.C.D. code*)	Number of deaths Observed O	 Expected E	O/E	P†
Leukaemia (204)	7	2·69	2·60	<0·03
Cancer of heavily irradiated sites (152–4, 171–6, 181)	61	47·28	1·29	<0·04
Multiple myeloma (203)	3‡	1·28	1·59	
Lymphomas (200–2, 205, 208)	4	3·13		—
Unknown primary (158–9, 165, 190–1, 196–9)	7	5·24	1·34	—
Cancer of breast (170)	14	26·86	0·52	<0·005
Other cancers	50	49·59	1·01	—
All neoplasms (140–239)	146	136·07	1·07	—
Aplastic anaemia (292·4)	2	0·25	—	<0·03
Coronary disease (420, 422·1)	104	105·48	0·99	—
Childbirth (640–689)	0	0·27	—	—
Diseases of genitals, breast, ovary, etc. (620–6, 630–7)	3	0·68	—	<0·04
Other causes	245	256·38	0·96	—
All causes	500	499·13	1·00	—

*International classification of disease—7th revision (WHO, 1957)

†The probability shown (P) is the probability that as large or larger a difference as that observed will be obtained by chance alone *in the direction actually observed*. The use of a "one-tailed" test is justified because the hypothesis being tested is that irradiation will increase the risk of cancer in irradiated sites and decrease the risk of cancer of the breast.

‡Includes one death which was certified as due to myeloid leukaemia but, on subsequent investigation of the patient's hospital notes, was found to be due to myelomatosis.

TABLE III

Number of deaths observed and expected by cause and time since first treatment

Cause of death		Time since first treatment (years) 0–4	 5–9	 10–14	 15–19	 20–24	 25+	Total five years or more after treatment*
Leukaemia	Obs.	0	3	2	2	0	0	7 (P<0·01)
	Exp.	0·35	0·47	0·61	0·62	0·44	0·19	2·33
	O/E	0·00	6·38	3·28	3·23	0·00	0·00	3·00
Cancer of heavily irradiated sites	Obs.	2	15	17	14	9	4	59 (P<0·004)
	Exp.	7·20	9·18	10·89	10·15	6·91	2·94	40·08
	O/E	0·28	1·63	1·56	1·38	1·30	1·36	1·47
Cancer of breast	Obs.	4	2	5	2	1	0	10 (P<0·003)
	Exp.	4·35	5·79	6·43	5·44	3·35	1·32	22·33
	O/E	0·88	0·35	0·78	0·37	0·30	0·00	0·45
Other cancers	Obs.	7	7	12	14	18	6	57
	Exp.	6·86	10·16	13·80	14·05	10·04	4·33	52·39
	O/E	1·02	0·69	0·87	1·00	1·79	1·39	1·09
All neoplasms	Obs.	13	27	36	32	28	10	133 (P<0·08)
	Exp.	18·94	25·60	31·73	30·26	20·75	8·79	117·13
	O/E	0·69	1·05	1·13	1·06	1·35	1·14	1·14
Coronary disease	Obs.	2	11	28	32	18	13	102
	Exp.	4·60	10·97	21·68	29·26	25·86	13·11	100·88
	O/E	0·43	1·00	1·29	1·09	0·70	0·99	1·01
Other causes	Obs.	50	35	47	53	50	15	200
	Exp.	33·84	41·24	52·27	56·97	48·01	25·25	223·75
	O/E	1·48	0·85	0·90	0·93	1·04	0·59	0·89
All causes	Obs.	65	73	111	117	96	38	435
	Exp.	57·38	77·81	105·68	116·49	94·62	47·15	441·76
	O/E	1·13	0·94	1·05	1·00	1·01	0·81	0·98

*See footnote (†) to Table II.

breast is notable only five years after the initial treatment, but the observed deaths from this cause remain below the expected number more than 20 years after the irradiation. Deaths from other cancers, coronary disease, and all other causes are close to the expected number of cases in each time period. We have previously commented on the higher than expected mortality from other causes in the first five years following treatment, for which we have no explanation.

The 27 women who received a second course of treatment for metropathia are included in Table III as being at risk to the end of the follow-up period. Exclusion of the period at risk subsequent to the second course makes only minor differences to the table. Eight of these women died, only one dying of cancer of a site in the radiation field (bladder).

The excess of cancers of the heavily irradiated sites, five or more years after treatment, is distributed fairly evenly over the individual sites as is shown in Table IV. The observed number of deaths from cancer of the ovary is close to that expected, but the variation in the ratio of observed to expected deaths between the sites is not statistically significant.

TABLE IV

DEATHS FROM CANCERS OF HEAVILY IRRADIATED SITES FIVE OR MORE YEARS AFTER IRRADIATION, BY PRIMARY SITE

Primary site of cancer (I.C.D. code)	Number of deaths Observed	Expected	Obs./Exp.
Intestines (152–153)	24	13·86	1·73
Rectum (154)	8	5·23	1·53
Uterus (171–174)	16	10·34	1·55
Ovary (175)	8	7·66	1·04
Other pelvic sites (176)	0	0·85	0·00
Bladder (181)	3	2·15	1·40
All heavily irradiated sites	59	40·08	1·47

The ratio of observed to expected deaths for cancers of the heavily irradiated sites decreases with time since treatment five or more years after irradiation (Table III and Table V) but this decrease is not statistically significant (X_1^2 (trend)$=0{\cdot}37$). Also shown in Table V is the excess of the observed deaths over the expected number in each period. The excess deaths may be regarded as an estimate of those deaths which may be attributed to irradiation. The excess deaths per 100,000 woman years at risk shows little variation at different time periods five or more years after treatment. The average for this period being 65 per 100,000 with 95 per cent confidence limits of 17 to 123 per 100,000 woman years at risk.

In Table VI we examine the mortality according to the age of the patient when first treated. The ratio of observed to expected deaths for cancers of the heavily irradiated sites increases with increasing age at first treatment, there being little excess risk in those treated under the age of 46 years. The trend, however, is not statistically significant (X_1^2 (trend$=3{\cdot}03$; $P<0{\cdot}09$).

However, in this situation, even a constant *relative* risk with respect to age at first treatment implies an increasing ***absolute*** excess risk with increasing age at first treatment, as the expected death rate, based upon national mortality statistics, from cancer of sites in the radiation field increases with age. This effect is demonstrated in Table VII, the number of deaths attributable to the radiation exposure per 100,000 woman years at risk increases from 17 in those aged less than 46 years at first treatment, to

TABLE V

NUMBERS OF OBSERVED AND EXPECTED DEATHS FROM CANCER OF THE HEAVILY IRRADIATED SITES SHOWN BY TIME SINCE TREATMENT AND YEARS AT RISK

		Time since first treatment (years)						Five years or more after treatment
		0–4	5–9	10–14	15–19	20–24	25+	
Deaths from cancer of heavily irradiated sites	Obs.	2	15	17	14	9	4	59
	Exp.	7·20	9·18	10·89	10·15	6·91	2·94	40·08
	O/E	0·28	1·63	1·56	1·38	1·30	1·36	1·47
Excess deaths	O–E	–5·20	5·82	6·11	3·85	2·09	1·06	18·92
Woman years at risk		10,079	9,643	8,780	6,321	3,333	1,131	29,208
Excess deaths per 10^5 woman years at risk		—	60	70	61	63	94	65

220 in those first treated at age 51 years or more. (X_1^2 (trend)$=5{\cdot}21$; $P<0{\cdot}03$). The women dying of leukaemia were treated at ages 43, 45, 45, 48, 49, 50 and 56 years respectively, but they are too few to make detailed analysis worth while.

A deficiency of deaths from cancer of the breast is seen regardless of the age at first treatment; the effect is least marked in those treated at ages 46–50 years but there is no clear evidence of a change with age at irradiation (Table VI).

The number of deaths from coronary disease shows no significant departure from the expected

TABLE VI

NUMBER OF OBSERVED AND EXPECTED DEATHS FIVE OR MORE YEARS AFTER IRRADIATION FOR SELECTED SITES SHOWN BY AGE AT FIRST TREATMENT

Cause of death		Age at first treatment (years) (mean age)		
		Less than 46 (42)	46–50 (48)	More than 50 (53)
Leukaemia	Obs.	3	3	1
	Exp.	1·07	0·90	0·37
	O/E	2·80	3·33	2·70
Cancer of heavily irradiated sites	Obs.	21	25	13
	Exp.	18·31	15·48	6·30
	O/E	1·15	1·61	2·06
Cancer of breast	Obs.	4	6	0
	Exp.	11·19	8·22	2·92
	O/E	0·36	0·73	0·00
Other cancers	Obs.	28	23	6
	Exp.	23·10	20·61	8·68
	O/E	1·21	1·12	0·69
All neoplasms	Obs.	56	57	20
	Exp.	53·66	45·21	18·26
	O/E	1·04	1·26	1·10
Coronary disease	Obs.	41	43	18
	Exp.	36·68	41·86	22·35
	O/E	1·12	1·03	0·81
Other causes	Obs.	95	75	30
	Exp.	86·09	89·40	48·26
	O/E	1·10	0·84	0·62
All causes	Obs.	192	175	68
	Exp.	176·42	176·47	88·86
	O/E	1·09	0·99	0·77

TABLE VII

DEATHS FROM CANCER OF HEAVILY IRRADIATED SITES FIVE OR MORE YEARS AFTER IRRADIATION

	Age at first treatment (years) (mean age)			Total
	Less than 46 (42)	46–50 (48)	More than 50 (53)	
Deaths from cancer of heavily irradiated sites (O)	21	25	13	59
Expected number of deaths (E)	18·31	15·48	6·30	40·08
Excess deaths (O–E)	2·69	9·52	6·70	18·92
Woman years of risk	16,126	10,038	3,044	29,208
Excess deaths per 10^5 woman years at risk	17	95	220	65

TABLE VIII

NUMBER OF OBSERVED AND EXPECTED DEATHS,* FIVE OR MORE YEARS AFTER IRRADIATION, FOR SELECTED SITES SHOWN BY ESTIMATED BONE MARROW DOSE.

Cause of death		Estimated bone marrow dose (rad) (mean dose)		
		Less than 125 (109)	125–149 (141)	150 or more (165)
Leukaemia	Obs.	2	3	2
	Exp.	0·89	1·16	0·25
	O/E	2·25	2·59	8·00
Cancer of heavily irradiated sites	Obs.	25	24	9
	Exp.	15·80	19·61	4·25
	O/E	1·58	1·22	2·12
Cancer of breast	Obs.	3	6	1
	Exp.	8·23	11·39	2·46
	O/E	0·36	0·53	0·41
Other cancers	Obs.	29	26	1
	Exp.	20·53	25·73	5·59
	O/E	1·41	1·01	0·18
All neoplasms	Obs.	59	59	13
	Exp.	45·46	57·89	12·55
	O/E	1·30	1·02	1·04
Coronary disease	Obs.	30	60	12
	Exp.	42·58	47·08	10·22
	O/E	0·70	1·27	1·17
Other causes	Obs.	82	93	20
	Exp.	97·17	102·38	21·85
	O/E	0·84	0·91	0·92
All causes	Obs.	171	212	45
	Exp.	185·21	207·36	44·62
	O/E	0·92	1·02	1·01

*The numbers in this table are not directly comparable with those in previous tables, as women receiving a second treatment course of radiation for metropathia have been withdrawn from the analysis at the date of the second course. This was necessary because of the difficulties associated with combining dose estimates from two or more treatment courses separated in time.

TABLE IX

EXCESS DEATHS* FROM LEUKAEMIA AND CANCER OF THE HEAVILY IRRADIATED SITES OCCURRING FIVE OR MORE YEARS AFTER IRRADIATION, SHOWN ACCORDING TO ESTIMATED BONE MARROW DOSE

	Estimated bone marrow dose (rad) (mean dose)			
	Less than 125 (109)	125–149 (141)	150 or more (165)	Total
Woman years at risk	10,548	15,071	3,238	28,857
Leukaemia excess deaths (observed–expected)	1·11	1·84	1·75	4·70
Excess deaths/10^5 woman years at risk	10·5	12·2	54·0	16·3
Cancers of heavily irradiated sites—excess deaths	9·20	4·39	4·75	18·34
Excess deaths/10^5 woman years at risk	87·2	29·1	146·7	63·6

*See footnote to Table VIII.

number at different ages at first treatment, but there is a slight, non-significant, tendency for the mortality ratio to decrease with increasing age. The ratio of observed to expected deaths from all causes shows a significant decrease with increasing age at first treatment (X_1^2 (trend)$=5{\cdot}82$; $P<0{\cdot}02$). This decrease is largely attributable to deaths from causes other than neoplasms or coronary disease (X_1^2 (trend)$=8{\cdot}50$; $P<0{\cdot}004$). This finding was unexpected and we have no explanation for it.

The estimated radiation dose to exposed organs has been made only for the bone marrow, using the method developed by the Committee on Radiological Hazards to Patients (1966). This dose is, however, likely to be approximately proportional to the dose received by the principal sites in the radiation field. An estimated bone marrow dose of between 70 and 190 rad was received by 99·4 per cent of patients during their initial treatment and the mean dose for the whole group of patients was 134 rad. Table VIII shows the distribution of observed and expected deaths for patients grouped in three divisions of estimated dose, and Table IX shows the excess deaths from leukaemia and from cancers of the heavily irradiated sites per 100,000 woman years at risk in each of the dose groups. The mortality from leukaemia increases with dose but a clear relationship is not apparent for cancers of the heavily irradiated sites; the numbers of excess deaths are too small in each group to allow firm conclusions. Overall, the excess death rate from leukaemia was 16·3 per 100,000 woman years at risk five or more years after treatment, and the mean marrow dose for all women was 134 rad. Thus, on the simplest assumption of a linear dose response relationship, we would estimate the average annual incidence of leukaemia attributable to radiation, five or more years after the radiation exposure, to be 1·22 per million women per year per rad (95 per cent confidence intervals are 0·13 to 3·13 per million women per year per rad). For the first 20 years after irradiation the excess rate is estimated to be 1·06 per million women per year per rad (95 per cent confidence intervals are 0·16 to 2·65).

In Table VIII, the ratio of observed to expected deaths from cancers of non-irradiated sites (excluding leukaemia and cancer of the breast) declines with increasing estimated bone marrow dose (X_1^2 (trend) $=6{\cdot}07$; $P<0{\cdot}02$). We have no explanation for this observation.

Details of the treatment received by the additional woman dying from leukaemia since the last report are as follows:

Case No. 10439

Aged 48 years, treated 1953 with one dose of 300 rad and one dose of 250 rad at one week's interval to two anterior and two posterior pelvic fields each 15×10 cms; mean marrow dose 139 rad. Erythroleukaemia diagnosed February 1971, died April 9, 1971.

DISCUSSION

In our previous publication (Doll and Smith, 1968) we reviewed the studies of cancer mortality following a radiation induced menopause that had been reported to that date. Since then a number of other studies have been described. Brinkley and Haybittle (1969) followed 277 women for between 15 and 25 years after an X-ray induced menopause. They found a threefold excess of cancers of the heavily irradiated sites five or more years after irradiation and an increase in deaths due to coronary or cerebrovascular disease, notable only in the first five years following treatment. No deaths from leukaemia were noted but only 0·24 were expected. These authors also studied cancer incidence data and found essentially the same results as from their study of mortality. There was no reduction in the incidence of breast cancer, which the authors suggest may have been due to the older age of their patients at the time of treatment; but the numbers involved were very small (five against 5·87 expected). Alderson and Jackson (1971) traced 2,049 patients treated with radium (15 per cent) or X rays (85 per cent) between 1946 and 1960. In the period of follow-up no excess was found of cancers of the heavily irradiated sites, but four cases of leukaemia were identified whereas only 1·8 were expected. All of the leukaemia deaths occurred five or more years after treatment and when this period only was considered the difference became statistically significant. A deficit of deaths from cancer of the breast was observed and coronary disease was elevated, though not significantly so. The results of these two studies and ours with respect to deaths from leukaemia and cancers of heavily irradiated sites are summarized in Table X. The data are tabulated according to the time since treatment in five-year periods. The findings in the three studies are essentially compatible and any differences may be due to the small numbers of deaths involved. Dickson (1969) has reported the follow-up of 4,010 women treated with radium for benign uterine haemorrhage between 1926 and 1966. An increased incidence of uterine carcinoma was found but there was no significant increase in cancer of other pelvic organs or of leukaemia. However, less than 50 per cent of the treated patients were adequately traced and thus interpretation of the findings is very difficult.

A contrary finding with respect to leukaemia induction is provided by studies of patients treated with X irradiation for cancer of the cervix. Simon *et al.* (1960) reported no increased leukaemia mortality among 71,000 patients treated with radium, but interpretation of this finding was made difficult because of incomplete follow-up of the population. Hutchison (1968), however, has reported a similar finding among 29,493 patients treated with radium and/or external X-ray therapy from 1960 onwards at 29 centres in an international study. These patients have been carefully followed and only four cases of leukaemia have been observed against about 5·5 expected. The expected number of cases in the period four or more years after treatment was only 2·7 and three cases were observed so that a possible fourfold increase in risk could be excluded but a threefold increased risk remained possible. The mean dose to the marrow for three-quarters of the patients was estimated to be from 300 to 1,500 rad. Based on the experience of the survivors of the Nagasaki and Hiroshima atomic bomb explosions and that of patients treated with X rays for ankylosing spondylitis, the International Commission on Radiological Protection (ICRP) (1966) has estimated

TABLE X

NUMBER OF DEATHS OBSERVED AND EXPECTED FROM LEUKAEMIA AND CANCER OF THE HEAVILY IRRADIATED SITES BY TIME SINCE FIRST TREATMENT, IN THREE BRITISH SERIES OF PATIENTS

		Time since first treatment (years)				
Cause of death	Authors	0–4 Obs./Exp.	5–9 Obs./Exp.	10–14 Obs./Exp.	15+ Obs./Exp.	5+ Obs./Exp.
Leukaemia	Doll and Smith (1975)*	0/0·35	3/0·46	2/0·60	2/1·24	7/2·31
	Alderson and Jackson (1971)†	0/0·31	3/0·37	1/0·36	0/0·36	4/1·09
	Brinkley and Haybittle (1969)	0/0·05	(not given)	(not given)	(not given)	0/0·19
	Combined series (Obs./Exp.)	0/0·71 (0·00)	6/0·83 (7·23)	3/0·96 (3·13)	2/1·60 (1·25)	11/3·59 (3·06)
Cancer of heavily irradiated sites	Doll and Smith (1975)*	2/7·14	15/9·10	17/10·79	26/19·77	58/39·66
	Alderson and Jackson (1971)	3‡/4·78	9/6·05	8/5·66	1/4·99	18/16·70
	Brinkley and Haybittle (1969)	2/0·79	(not given)	(not given)	(not given)	9/3·06
	Combined series (Obs./Exp.)	7/12·71 (0·55)	24/15·15 (1·58)	25/16·45 (1·52)	27/24·76 (1·09)	85/59·42 (1·43)

*See footnote to Table VIII.

†Data shown for leukaemia relate only to patients treated with X rays.

‡Excludes five patients with malignancy at time of radiation.

that 1 rad to the whole body might be expected to produce 20 cases of leukaemia per million persons in the first 10 to 20 years after exposure. If we assume that the mean marrow dose to three-quarters of the patients in Hutchison's series was 1,000 rad (Hutchison, 1968) and consider their experience four or more years after treatment, then a minimal estimate of the expected number of cases of leukaemia would be 1,000 (rad)$\times$3/4$\times$31,479 (the number of years at risk four or more years after treatment)$\times 10^{-6}$ (assuming an induction rate for leukaemia of $1/10^6$ persons/rad/year)=16 cases. Only three cases were observed in this period, suggesting that exposure to radiation in the treatment of cancer of the cervix is less effective in inducing leukaemia than the exposures received in Hiroshima and Nagasaki and by ankylosing spondylitics.

Dickson (1972) has also recently reported on the follow-up of 923 women surviving more than five years after radium treatment for cancer of the cervix. Two deaths from leukaemia were observed whereas 1·1 was expected. Wagoner (1969, 1970) observed no excess of leukaemia among 7,835 women treated with radium and X rays for primary uterine cancer (12 cases of leukaemia observed and 9·50 expected). However, he also studied two series of patients treated for benign gynaecological disorders with radium. Among 1,803 patients treated in Massachusetts he observed 10 deaths from leukaemia against 3·6 expected and, in a similar series in Connecticut, nine cases of leukaemia were observed against 2·8 expected.

In the present study we have observed an excess death rate from leukaemia five or more years after exposure of 1·2 per million woman years at risk per rad, an amount in accord with that estimated by the ICRP. The most likely explanation for the apparent discrepancy in the effects of radiation among cancer of the cervix patients relates to the difference in the distribution of dose throughout the bone marrow. Hutchison (1968) has demonstrated that the radiation treatment of cervical cancer is such that a small proportion of the bone marrow, in the pelvic region, receives a very large dose and the fall off in dose to the marrow is rapid with increasing distance from the pelvic area. A very heavy dose to the pelvic marrow is likely to result in cell death rather than leukaemogenesis and, because of the rapid fall-off in dose with distance from the pelvis, the mean dose to those cells not destroyed by the radiation may be relatively small. Patients treated for metropathia, however, receive a dose to the pelvic marrow which is considerably less than that given for the treatment of the cancer of the cervix, and thus the destructive effect on the bone marrow is likely to be substantially less. The importance of this cell destruction effect in re-assessing leukaemia dose response relationships has recently been stressed by Mole (1973, 1975).

Our series is too small to hope to show a significant dose-response relationship for leukaemia though there is some indication of such an effect in Table IX. There is, however, little indication of this for cancers of the heavily irradiated sites. The excess of these latter cancers is statistically significant and most marked five or more years after treatment. The distribution of deaths among different sites in the radiation field shows some variation (Table IV) though the variation among the mortality ratios is not statistically significant. The limitation of the increased mortality from non-genital cancers to those in the radiation field strongly suggests that the excess is an effect of the radiation rather than directly related to the presenting condition, as has been suggested by Senyszin (1970). The excess risk does not seem to vary with the time since treatment after the first five years, remaining at about 65 deaths per 100,000 woman years at risk up to 20 years after treatment (Table V). This finding contrasts with that observed among patients treated for ankylosing spondylitis, who overall show a similar excess risk of dying from cancers of heavily irradiated sites (about $60/10^5$ person/year), but whose excess risk shows a steady increase nine or more years after radiation (Court Brown and Doll, 1965). This late increase may, however, be due, at least in part, to patients being retreated with X rays. Among the atomic bomb survivors, the excess mortality from cancers, other than leukaemia, also shows a late rise 20 years after exposure (Jablon and Kato, 1972), and it may be that our results are atypical because of the paucity of numbers. If, however, a progressive increase in numbers cannot be ruled out, the totality of evidence suggests that its duration may be less than has been suspected.

The suggestion of a relationship between age at treatment and the risk of developing cancers of the heavily irradiated sites (Table VII) is in accord with similar observations among atomic bomb survivors. Among those exposed to 100 rad or more the excess risk of cancers, other than leukaemia, was about four times higher in those exposed after the age of 50 years compared with those exposed at younger ages (Jablon, 1973). It should be noted that our findings cannot be attributed to an association between age at first treatment and the radiation dose employed. For women first treated at ages less than 35, 35–39, 40–44, 45–49, 50–54, and 55 years or older, the mean marrow doses were, respectively, 131, 130, 133, 135, 134 and 137 rad.

The decreased death rate from cancer of the breast associated with an artificially induced menopause (Table II) has been observed often. The reasons for it have been discussed by Feinleib (1968) and Trichopoulos *et al.* (1972). Of particular interest is the observation in our series that the protective effect against breast cancer appears to be present in women treated after the age of 50 years. In general, women in this age group might be expected to show a mortality rate from breast cancer *higher* than that based on national mortality statistics as a late natural menopause has been associated with an increased risk of developing cancer of the breast (Trichopoulos *et al.*, 1972). Thus the deficiency observed suggests that the sterilization induced by radiation is producing an effect on ovarian function, in relation to the development of breast cancer, which is different from the corresponding effect of a natural menopause, or of a surgically induced menopause (Trichopoulos *et al.*, 1972).

The number of deaths from coronary disease is close to that expected even for women treated before the age of 46 years. In similar series of patients, Alderson and Jackson (1971) also failed to find a significant excess risk of coronary disease, while Brinkley and Haybittle (1969) found a significant excess although only in the first five years after radiotherapy. Most of the women in these series were treated at an age closer to their natural menopause than those women with a premature menopause reported by Robinson *et al.* (1959) and Sznajderman and Oliver (1963), in whom an increased incidence of coronary disease was observed.

ACKNOWLEDGMENTS

We thank Professor R. MacWhirter, Dr. E. F. Ridley and Dr. W. C. Swanson for permission to study the patients treated in their departments. Miss Zoe Fotheringham was responsible for the follow-up of the patients in this study and we are greatly indebted to her for the care and perseverance which she devoted to this task. Diana Bull, Barbara Crossley and Paul Humphreys kindly gave coding, computing and statistical assistance. The work was initiated and supported by a grant from the Medical Research Council.

REFERENCES

Alderson, M. R., and Jackson, S. M., 1971. Long term follow-up of patients with menorrhagia treated by irradiation. *British Journal of Radiology*, *44*, 295–298.

Brinkley, D., and Haybittle, J. L., 1969. The late effects of artificial menopause by X radiation. *British Journal of Radiology*, *42*, 519–521.

Committee on Radiological Hazards to Patients, 1966. Final report of the committee on radiological hazards to patients. Ministry of Health and Scottish Home and Health Department (H.M.S.O., London).

Court Brown, W. M., and Doll, R., 1965. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *British Medical Journal*, *2*, 1327–1332.

Dickson, R. J., 1969. The late results of radium treatment for benign uterine haemorrhage. *British Journal of Radiology*, *42*, 582–594.

1972. Late results of radium treatment of carcinoma of the cervix. *Clinical Radiology*, *23*, 528–535.

Doll, R., and Smith, P. G., 1968. The long term effects of X irradiation in patients treated for metropathia haemorrhagica. *British Journal of Radiology*, *41*, 362–368.

Doll, R., 1971. Cancer following therapeutic external irradiation. In: Clark, R. L., Cumley, R. W., McCay, J. E., and Copeland, M. M., eds. *Oncology* 1970: Proceedings of the Tenth International Cancer Congress. Vol. 5. Environmental causes, pp. 1–28 (Year Book Medical Publishers, Chicago).

Feinleib, M., 1968. Breast cancer and artificial menopause: a cohort study. *Journal of the National Cancer Institute*, *41*, 315–339.

Hutchison, G. B., 1968. Leukaemia in patients with cancer of the cervix uteri treated with radiation. A report covering the first five years of an international study. *Journal of the National Cancer Institute*, *40*, 951–982.

International Commission on Radiological Protection, 1966. The evaluation of risks from radiation. *ICRP Publication 8* (Pergamon Press, Oxford).

Jablon, S., and Kato, H., 1972. Studies of the mortality of A-Bomb Survivors. 5. Radiation dose and mortality, 1950–1970. *Radiation Research*, *50*, 649–698.

Jablon, S., 1973. The origin and findings of the Atomic Bomb Casualty Commission. U.S. Department of Health Education and Welfare, PHS, FDA, Bureau of Radiological Health, DHEW Publication No. (FDA) 73–8032.

Mole, R. H., 1973. Late effects of radiation carcinogenesis. *British Medical Bulletin*, *29*, 78–83.

1975. Ionizing radiation as a carcinogen: practical questions and academic pursuits. *British Journal of Radiology*, *48*, 157–169.

Robinson, R. W., Higano, N., and Cohen, W. D., 1959. Increased incidence of coronary disease in women castrated prior to the menopause. *Archives of Internal Medicine*, *104*, 908–913.

Senyszyn, J. J., 1970. The late effect of artificial menopause by X radiation. *British Journal of Radiology*, *43*, 224.

Simon, N., Brucer, M., and Hays, R., 1960. Radiation and leukaemia in cancer of the cervix. *Radiology*, *74*, 905–911.

Sznajderman, M., and Oliver, M. F., 1963. Spontaneous premature menopause ischaemic heart-disease and serum lipids. *Lancet*, *1*, 962–965.

Trichopoulos, D., MacMahon, B., and Cole, P., 1972. Menopause and breast cancer risk. *Journal of the National Cancer Institute*, *48*, 605–613.

Wagoner, J. K., 1969. Paper presented at a meeting of the American Public Health Association, reported in *Doll* (1971).

1970. Leukaemia and other malignancies following radiation therapy for gynecological disease. Unpublished Doctoral Thesis, Harvard School of Public Health, Boston.

World Health Organization, 1957. Manual of the international statistical classification of disease, injuries and causes of death: seventh revision (World Health Organization, Geneva).

1967. Manual of the international classification of diseases, injuries and causes of death: eighth revision (World Health Organization, Geneva).

1976, *British Journal of Radiology*, *49*, 233–237 MARCH 1976

The ventricular-brain ratio using planimetric measurement of EMI scans

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(*Received June, 1975*)

ABSTRACT

A correlation has been shown between the cross-sectional area of the cerebral ventricular system and the cross-sectional area of the brain in 62 patients, using the EMI Scanner. The percentage ratio has been abbreviated to VBR. The patients were divided into normal, equivocal, cerebral atrophy and hydrocephalus, according to their PEG's. The measurements were obtained by the use of a planimeter and by outlining the ventricular and cerebral perimeters from the EMI Polaroid pictures.

The VBR was found to be approximately five in those patients without detectable pathology, about seven in equivocal cases, and above ten in abnormal cases (atrophy, hydrocephalus). The hydrocephalic readings were generally higher than those for cerebral atrophy.

Attempts have been made in the past to establish a relationship between the cerebral ventricular and skull or brain sizes in the normal and abnormal (cerebral atrophy, ventricular enlargement) (Evans, 1942; Schiersmann, 1952). However, the findings are subject to the limitations imposed by the variations in cranial symmetry and shape. When pneumoencephalography (PEG) was introduced into this assessment, added objections to the accuracy were raised as to the sites of measurement and increase in ventricular size following the introduction of air (Probst, 1973).

With the advent of computerized transverse axial tomography of the brain (EMI-Scanner) (Hounsfield, 1973; Ambrose, 1973) it became possible to assess the association between the true ventricular and cerebral cross-sectional areas. Previously these measurements were made using the coronal plane and, accordingly, the antero-posterior projection on PEG. With the EMI scanning technique "cuts" are made in the horizontal plane. This permits an overall view of the cerebral ventricular system without the problem of superimposition of the various parts seen in PEG.

To date, ventricular size on EMI scanning is assessed in two ways:

(1) subjectively, by the investigator, as to whether or not it appears normal or enlarged on viewing the Polaroid pictures, and

(2) objectively, by the time-consuming method of using the computer print-out.

The area representing the ventricular system is examined for density numbers relating to cerebrospinal fluid (−2 to +10) and the perimeter of the ventricle mapped out.

In this series we have attempted to establish a correlation between ventricular and cerebral cross-sectional areas for the normal and abnormal and to decide on an upper limit of normality. This was accomplished using a planimeter and 1 mm squared paper to measure the ventricular and cerebral areas from the EMI scanner Polaroid pictures. From this the ventricular-brain cross-sectional area percentage ratio (VBR) was computed.

MATERIAL AND METHOD

Sixty-two patients at The National Hospital, Queen Square were selected on the basis of having had successful PEG's and EMI scans. The PEG results enabled classification of the patients into normal, equivocal and abnormal in terms of ventricular size and loss of cerebral tissue. The series consisted of 33 males and 29 females, with an average of 44 years (age range 1–73 years). Those cases of cerebral atrophy were of the generalized type.

The final clinical diagnosis in the 62 cases considered was as shown in Table I.

TABLE I

No pathology detected	19
Atrophy	
Cerebral	20
Cerebro-cerebellar	4
Hydrocephalus	
Normal pressure	6
Aqueduct stenosis	1
Infratentorial tumours	
Cerebello-pontine	3
4th ventricular	1
Others	
Syphilis of CNS	1
Migrainous headache	2
Benign intracranial hypertension	1
Boxer's encephalopathy	1
Disseminated sclerosis	2
Neurotic depression	1

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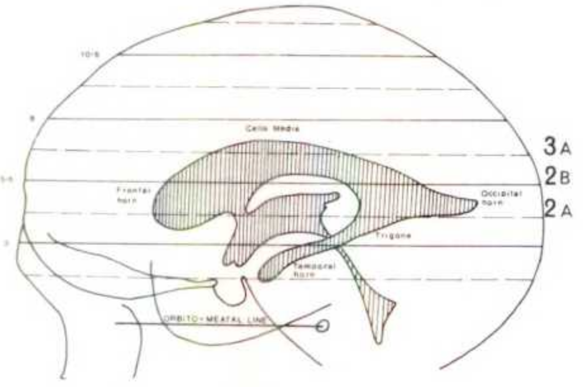

FIG. 1.
Diagram to show the level of the EMI "cuts" as referred to in the text.

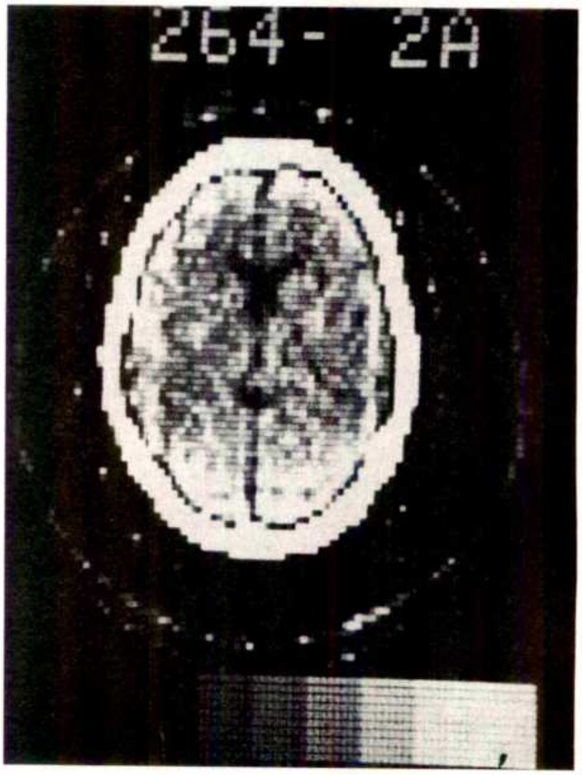

FIG. 2.
EMI Polaroid picture of a normal ventricular system from "cut" 2A. The frontal horns, lateral ventricles and 3rd ventricle are clearly seen.

EMI-Scanner

The principle and technique of computerized axial tomography has been fully covered by Hounsfield (1973) and Ambrose (1973). In this series the matrix used was that of 80×80, where each cell measured 3×3 mm in the transverse plane and had a depth of 8 or 13 mm, according to the original beam width (EMI Ltd., 1973). For our purpose only "cut" 2A or 2B and, occasionally, 3A was used (see Fig. 1), that is, one "cut" which optimally represented the ventricular system.

Technique of measurement

For each case, using the EMI Polaroid picture, the perimeter of the brain and visible ventricular system was measured using a planimeter (OTT 9541–32, West Germany). This instrument measures the area of a plane figure when a tracer is moved along the perimeter. In the normal this usually meant that the anterior horns and the bodies of the lateral ventricles and the 3rd ventricle were measured. In those cases of hydrocephalus, and in some of cerebral atrophy, other parts of the ventricular system may also be visible.

Some difficulty is experienced in exactly localizing the extent of the ventricular perimeter according to the values on the Polaroid pictures. This is dependent upon how much of the ventricle is included in the cut, and obviously varies according to what percentage of the cell is occupied by cerebrospinal fluid or cerebral tissue. An arbitrary range of density figures has been used and extends from -2 to $+10$. In some cases, where the outline of the ventricular system was in doubt, reference was made to the printout. For a fuller explanation of this difficulty, the reader is referred to the section "Evaluation of computerised tomograms" in Gawler *et al.* (1975).

Once the technique of planimetric measurement had been mastered, the time taken to measure the cross-sectional areas was approximately ten minutes per case.

The measurements were carried out on ten separate occasions for each picture and the average reading taken. As a means of verification, the outlines of the visible ventricular system and of the brain perimeter were traced on to millimetre squared paper and the cross-sectional area so assessed. The brain cross-sectional area was uncorrected for ventricular area.

The percentage ventricular-brain cross-sectional area ratio is expressed by:

$$\frac{\text{ventricular cross-sectional area}}{\text{brain cross-sectional area}} \times 100$$

For the purpose of simplicity, we refer to this equation as the VBR. Because the measurement is given as a ratio, the minification factor of the Polaroid picture does not here obtain.

RESULTS

The series was divided into four main groups (no detectable pathology, equivocal, atrophy, hydrocephalus) according to the assessment by PEG. Figures 2, 3 and 4 give examples of the EMI Polaroid picture from the sub-groups. The brain and ventricular perimeters have been copied on to millimetre squared paper in one instance, to show how the square counting method was used to verify the results obtained by planimetry (Fig. 5). No significant difference was found between the two methods.

A complete analysis of the results is presented in Table II.

DISCUSSION

The relationship of the size of the cerebral ventricular system to that of the brain appears seldom to have been investigated. An extensive review by Last and Tompsett (1953) using resin ventricular casts is the most detailed. They fully investigated 24 normal adult (and five fetal) brains. The overall shrinkage factor of 1–2 per cent of cast material and formalized brain lends a high degree of accuracy to their results. The average ventricular system capacity lay at 22·4 ml. which, against an average brain volume of 1,355 ml., gave a ratio of 0·016. This, of course, assesses a three-dimensional aspect of the complete ventricular system.

Two-dimensional ratios are those of Evans (1942) and Schiersmann (1952) who compared the span of parts of the lateral ventricles to the diameter of the skull, using the antero-posterior PEG view.

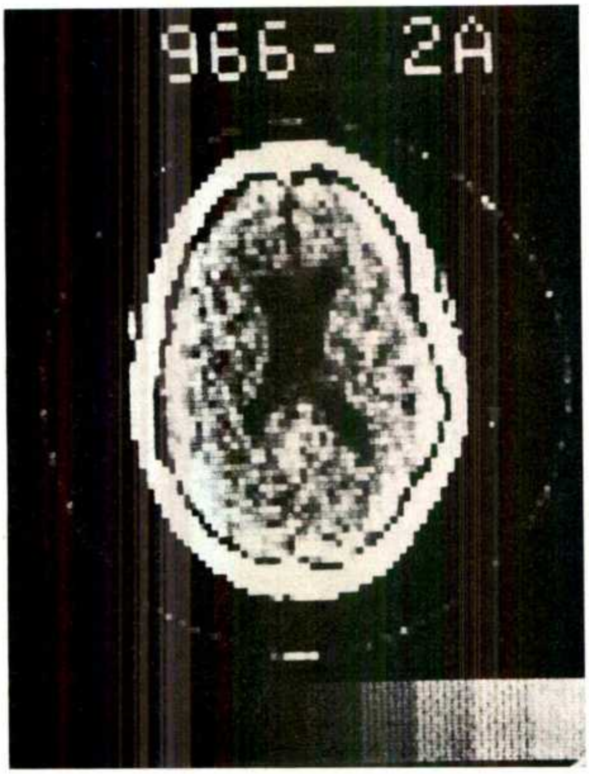

FIG. 3.

EMI Polaroid picture of cerebral atrophy from "cut" 2A showing enlargment of the lateral ventricles and increase in the size of the subarachnoid space.

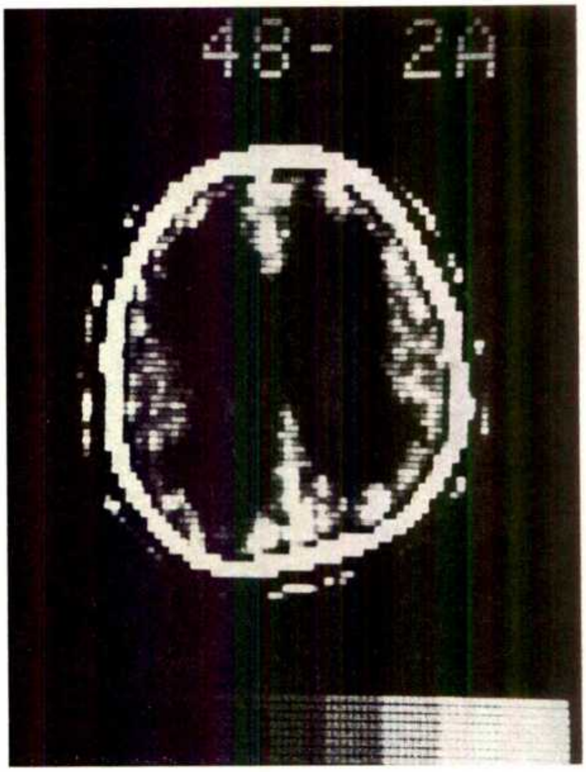

FIG. 4.

EMI Polaroid picture of gross hydrocephalus, with greatly enlarged lateral ventricles—"cut" 2A.

Echoencephalography (A mode) has been successfully used, particularly in those under one year of age, to assess the size of the cerebral ventricles. The same reliability does not obtain for those over that age group (Sjögren, 1967; Kazner and Hopman, 1973).

The EMI-Scanner allows easy assessment of the ventricular cross-sectional area without the use of invasive techniques and contrast materials, but, to date, no mention has been made of such a quantitative analysis. The ratios obtained in this preliminary report relate the cross-sectional area of the ventricular system to that of the brain as best seen on a particular "cut" mentioned in "Material and Method". The size of the normal ventricular system is variable and is dependent on numerous factors (Evans, 1942; Schiersmann, 1952; Last and Tompsett, 1953; Bull, 1961), as is also shown by our one normal VBR of 8·8. However, this does not detract from the value of the ratio as shown by the standard deviation of 1·33 and standard error of 0·32.

It is appreciated that, in measuring the ventricular cross-sectional area in the normals, similar parts of the system are taken into account in each case. However, in patients with atrophy or hydrocephalus the extent of the ventricular system entering into the calculation varies from the normal, and possibly even from case to case. This is dependent upon the fact that, with the ventricular enlargement, more and more of the cerebral ventricular volume is encompassed by the cells of the EMI unit scanning the particular "cut".

The results suggest a normal VBR of approximately five, equivocal cases seven, and abnormals above ten. The VBR for hydrocephalus is, overall, higher than for cerebral atrophy.

TABLE II

THE VENTRICULAR-BRAIN CROSS-SECTIONAL AREA PERCENTAGE RATIO (VBR)

	Pneumoencephalogram evaluation			
	No pathology (17 patients)	Equivocal (10 patients)	Atrophy (24 patients)	Hydrocephalus (11 patients)
VBR	3·3	5·4	15·3	35·3
	3·8	7·1	10·2	19·0
	4·2	9·6	14·4	89·0
	4·6	5·7	10·5	19·5
	4·9	6·7	9·3	17·0
	4·3	7·8	9·4	14·3
	4·8	8·5	10·0	20·3
	3·9	4·5	11·3	35·8
	4·3	7·7	22·0	52·0
	4·8	4·0	13·1	73·0
	5·0		9·7	14·3
	4·5		20·0	
	5·9		10·0	
	3·3		14·4	
	8·8		10·6	
	2·7		11·3	
	4·9		29·0	
			11·6	
			17·4	
			12·4	
			12·0	
			12·5	
			10·4	
Range	2·7–8·8	4·0–9·6	9·3–29·0	14·3–89·0
Mean	4·59	6·70	13·23	35·41
Standard deviation	1·33	1·79	4·72	25·58
Standard error	0·32	0·57	0·96	7·71

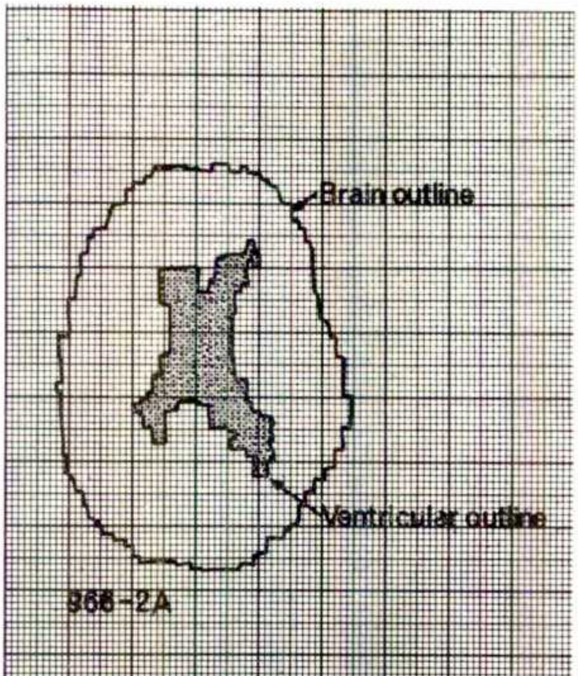

FIG. 5.

Planimetric outline of the ventricles and brain drawn on to millimetre squared paper from Fig. 3. The dotted area corresponds to the number of squares occupied by the lateral ventricles and represents its cross-sectional area. To obtain the VBR, this is divided by the brain cross-sectional area and the result multiplied by 100.

It should be stressed that, although quantitative measurements are used in calculating the VBR, the figures do not reflect the "true" measurement of the ventricles. However, the usefulness of the ratio so obtained is evident.

ACKNOWLEDGMENTS

We wish to thank Dr. G. H. du Boulay and Dr. J. Gawler for their assessment of the pneumoencephalograms, their advice, and for allowing us to use their material.

REFERENCES

AMBROSE, J., 1973. Computerized transverse axial scanning (tomography): Part 2. Clinical application. *British Journal of Radiology*, *46*, 1023–1047.

BULL, J. W. D., 1961. The volume of the cerebral ventricles. *Neurology*, *11*, 1–9.

EMI Limited, 1973. *EMI-Scanner. A new perspective on brain disease.* First brochure issued by EMI Limited, Middlesex, England.

EVANS, W. A., 1942. An encephalographic ratio for estimating ventricular enlargement and cerebral atrophy. *Archives of Neurology and Psychiatry*, *47*, 931–937.

GAWLER, J., DU BOULAY, G. H., BULL, J. W. D., and MARSHALL, J., 1976. Computerised tomography (The EMI-Scanner). A comparison with pneumoencephalography and ventriculography. *Journal of Neurology, Neurosurgery and Psychiatry* (in press).

HOUNSFIELD, G. N., 1973. Computerized transverse axial scanning (tomography): Part 1. Description of system. *British Journal of Radiology*, *46*, 1016–1022.

KAZNER, E., and HOPMAN, H., 1973. Possibilities and reliability of echoventriculography. *Ultrasound in Medicine and Biology*, *1*, 17–32.

LAST, R. J., and TOMPSETT, D. H., 1953. Casts of the cerebral ventricles. *British Journal of Surgery*, *40*, 525–543.

PROBST, F. P., 1973. Gas distension of the lateral ventricles at encephalography. *Acta Radiologica* (*Diag.*), *14*, 1–4.

SCHIERSMANN, O., 1952. *Einführung in die Encephalographie.* 2. Aufl. (Thieme Verlag, Stuttgart).

SJÖGREN, I., 1967. Echoencephalography in paediatric practice with special regard to measurement of the ventricular size. *Acta paediatrica scandinavica; Supplement 178.*

Book reviews

Tumor und Temperatur. By Dr. Franz Dietzel, pp. ix+253, 1975 (Munich-Berlin-Vienna, Urban a Schwarzenberg), DM45.

It has been known for more than half a century that general hyperthermia can sometimes be followed by tumour regression, and also that some cancers can be destroyed by specific heat damage on malignant tissue in situations where it is possible to apply sufficient thermal energy without causing unacceptable general overheating. There are a number of documented cures of cancers of the limbs and of the penis. These observations have in recent years led to laboratory experiments on the effects of heat on normal and abnormal cells and tissues by *in-vivo* and *in-vitro* studies. The subject remains a controversial one, but there are pointers that thermal methods might become more often employed in cancer treatment. One encouraging observation is the enhancement of the biological effect of radiation by elevation of temperature which in itself has no damaging effect on normal or abnormal tissues and that this enhancement applies particularly to anoxic cells.

This book is a comprehensive and systematic survey of the international literature up to the beginning of 1975—over 800 pages. The author has succeeded well in his aim of giving a clear and unbiased exposition of the present state of thermo-biology and cancer.

M. HULBERT.

Hematologische Funktionsdiagnostik in der Radiologie. By Bruno Chone, pp. xii+194, illus. 1974 (West Berlin, Urban & Schwarzenberg), DM.58.

There are a number of methods for the monitoring of the haematopoietic system of patients who are being treated by wide-beam irradiation, or by cytotoxic-drugs, or by a combination of both; these methods also apply to the surveillance of radiation-exposed personnel. The author gives a description and evaluation of these tests, and he deals, for instance, with clinical peripheral blood-count, bone-marrow examination, isotope investigation of blood-cell turnover and of iron metabolism, assessment of the haematological response to stimulation by prednisone or by polysaccharides or ethiocholanolone. There is also a chapter on an automated method for assessing the volume-distribution of circulating leucocytes which the author has found to be a very sensitive indicator. It remains to be seen how far these methods will prove to be superior to the ordinary blood-count in the clinical management of patients.

The book is clearly written and set out with many illustrations and a comprehensive bibliography of the international literature. The author has succeeded in his aim of giving a full account of the subject which is of particular interest to medical or radiological oncologists and to their haematological colleagues.

M. HULBERT.

1976, *British Journal of Radiology*, *49*, 238–243

Ultrasonic echo imaging of tissues: instrumentation

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(*Received March, 1975*)

Abstract

The ultrasonic pulse-echo principle is capable of providing detailed information, of considerable potential diagnostic value, on the structure of soft tissues in relation to pathology, but the present generation of ultrasonic scanners does not fully exploit this possibility. The paper discusses the principal measures necessary to achieve tissue structure visualization and quantitative characterization and describes a clinically functioning system that has been built for this purpose with particular relation to cancer diagnosis. Examples of the application of the system are given in this and an accompanying paper.

Hitherto the development of pulse-echo ultrasonic diagnosis has been strongly influenced by the idea that useful echoes would normally only arise from rather large, flat interfaces, such as those presented by the brain midline and fetal skull, which are considered to reflect specularly (*i.e.* directionally). As a result, equipment and techniques have developed in a direction that was intended to facilitate the drawing of clear pictures of organ outlines, with suppression of the smaller echoes which arise from within the major organ boundaries and which were considered to be confusing to the outline pictures. This approach happens also to be convenient technically, since it does not call for very great sensitivity in the equipment and it avoids the need to display and record the very wide range in amplitude that occurs between the various echoes from gross and detailed anatomical structure. Almost all the ultrasonic scanners in common use today adopt this approach and many employ, as their only display system, a storage cathode-ray tube of very limited grey-scale capability.

The organ-outlining approach has proved its value in obstetrics scanning, where fetal maturity, multiple gestation and position of the fetus and placenta are of major interest, but even here the value of providing grey-scale display for visualizing details of fetal anatomy has been very strikingly demonstrated by Kossoff, Garrett and Radovanovich (1974). There are many diagnostically important situations, however, particularly in cancer, where indications about the condition of the tissue itself are of equal or greater importance than knowledge of organ boundary location. Here ultrasound may have a very useful role to play and, to exploit this, it becomes necessary to re-think from first principles some of the considerations underlying ultrasonic scanner design. This is the subject of the present paper.

The Echo Formation Process

Little is known in detail about the processes by which complex structures, such as those of the human anatomy, give rise to acoustic echoes. Plane interfaces, of extent greater than the width of the ultrasonic beam, reflect specularly, and it is on this basis that the technique of "compound scanning" (examining from a wide range of aspect angles and selecting only large, normally reflected echoes) is often used. Small single targets, however, tend to reflect uniformly in all directions and early observations of the echoes from the internal structure of an organ such as liver suggested that these might be more nearly omnidirectional than specular. In fact recent work on the ultrasonic scattering properties of some actual human tissues (Hill, 1974) has shown that the echo amplitude from a small tissue volume fluctuates with aspect angle in a manner that may be characteristic of the tissue structure and thus the tissue type. At a given aspect angle the mean amplitude of echoes from a region of tissue may also be characteristic of the tissue type and this criterion has been used, for example, by Mountford and Wells (1972) to differentiate cirrhotic from normal liver. As already mentioned, the variation in echo level between the strongest and weakest targets of interest (*e.g.* large soft tissue/bone interfaces on the one hand and suspended debris within a bladder on the other) may be very large, amounting to some 50 dB (a factor of 300 in amplitude).

In terms of scanning system design this situation suggests that, although conventional compound scanning will often have an important role in organ outlining, a promising complimentary approach will be to arrange to scan regions of the body in a systematic manner such that appropriate acoustic characteristics of the tissue may be measured and recorded for each physically resolvable volume in the region. The approach outlined here involves making much fuller use than has been general hitherto of the very rich supply of information that the basic pulse-echo principle is capable of generating. In fact many of the limitations of existing scanning systems can be seen to stem from the technical problems of displaying, recording and conveying to the diagnostician anything like the full amount of information potentially available. This must be a major consideration in future scanner design and suggests, *inter alia*, the use of fast digital information storage and processing.

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* On leave from National Acoustics Labs., Sydney, Australia.

THE SCANNING SYSTEM

We have recently built an ultrasonic scanning system which has been designed on the basis of the above considerations. Although intended for use primarily in investigations related to cancer diagnosis and treatment, it has potential applications in a wide variety of fields and has already been used very effectively, for example, for placental localization and estimation of fetal maturity. A report on some clinical applications in cancer diagnosis is given in an accompanying paper (Taylor and McCready, 1976).

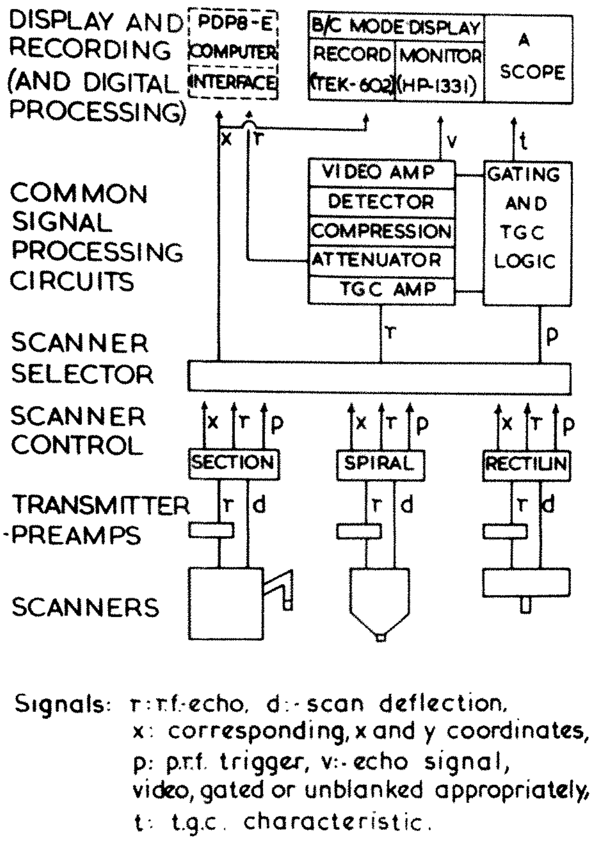

DISPLAY AND RECORDING (AND DIGITAL PROCESSING)
PDP8-E COMPUTER INTERFACE
B/C MODE DISPLAY
RECORD (TEK-602)
MONITOR (HP-1331)
A SCOPE
x
r
v
t
COMMON SIGNAL PROCESSING CIRCUITS
VIDEO AMP
DETECTOR
COMPRESSION
ATTENUATOR
TGC AMP
GATING AND TGC LOGIC
r
p
SCANNER SELECTOR
SCANNER CONTROL
x r p
SECTION
SPIRAL
RECTILIN
TRANSMITTER -PREAMPS
r d
SCANNERS
Signals: r: r.f.-echo, d: scan deflection,
x: corresponding, x and y coordinates,
p: p.r.f. trigger, v: echo signal,
video, gated or unblanked appropriately,
t: t.g.c. characteristic.

FIG. 1.
Outline diagram of system for ultrasonic tissue imaging.

In the design of this system major emphasis has been placed on the need to preserve, as far as possible, the full information content of the echo signals, from their point of origin in the patient through to the final display and permanent record. Furthermore, by use of a modular design, the equipment has been arranged so that investigations of different anatomical regions can be carried out using the scanning geometries and corresponding scanning mechanisms best suited to the purpose. The system that has been constructed on this basis is shown in outline in Fig. 1 and some details of the main components are given in the following sections.

SCANNING HEADS

The system is designed to accommodate several different mechanical scanning-heads in addition to a hand-held transducer for A-mode and M-mode operation. In order to reduce the effect of cable loading on pulse shape and noise, each scanning-head is provided with its own integrated circuit-transmitter, which supplies a fast 50 V pulse to the transducer, and a low-noise preamplifier. Movement of each scanning-head is controlled from a specific module on the control console in such a way that additional scanning-heads may be included, or changes made to an existing head, without disturbing the rest of the system. Each scanning-head, working together with its control module, generates an r.f. echo signal, appropriate "X" and "Y" deflection signals for the display system and also (except when under computer control) its own pulse-trigger signals.

The scanning-head that has been used hitherto for most of our clinical scanning is a conventional section scanner (Kretz) modified by addition of a transmitter/preamplifier together with an optional facility for deriving a pulse repetition rate proportional to the angular speed of movement of the transducer. The scanner is normally used with a weakly focused transducer of measured (zero crossing) frequency 2·85 MHz, which has a 10 dB echo beamwidth of 2·5 mm over the range of target distances from 50 to 120 mm. This arrangement provides sufficient sensitivity for scanning a full abdominal cross-section under normal conditions, the system noise level at 100 mm from the transducer face being 83 dB relative to the echo from a 10 mm diameter steel sphere (Lypacewicz and Hill, 1974). The peak pressure amplitude in the transmitted beam, measured at 100 mm from the transducer face, is 1·5 MPa (15 bar).

A number of scans obtained with this device in the course of clinical investigations are reported in an accompanying paper (Taylor and McCready, 1976).

In addition to this conventional scanning-head, two other scanners have been used with the system, primarily on an experimental basis hitherto but with some clinical application. One of these is a rectilinear scanner, working through a water-bath, in which the beam axis is normal to the plane of the rectilinear raster. This is suitable for examining superficial organs and has been used successfully both on breasts and testes in a configuration where the beam is directed vertically upwards from the bottom of a water-bath and the organ being examined is immersed above it. It has also been used for scanning thyroids in an arrangement where the beam is directed downwards through an open-topped, water-filled bag whose membrane is in contact with the patient's neck. Examples of section scans taken in this manner are shown in Figs. 2 and 3 and in Figures 11 and 12 of the accompanying paper (Taylor and McCready, 1976).

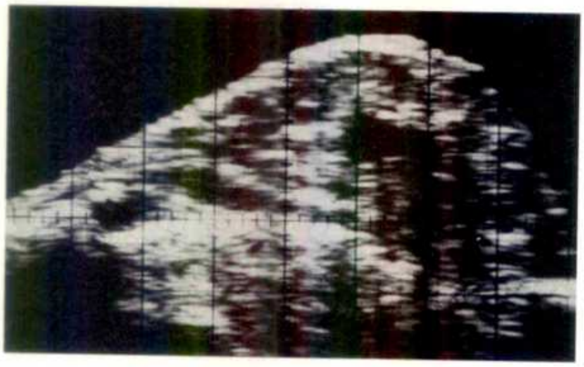


FIG. 2.

Rectilinear section scan of left breast, taken through a water-bath (see text), showing a centrally positioned cyst, surrounding glandular and fatty tissue, and underlying rib cage.

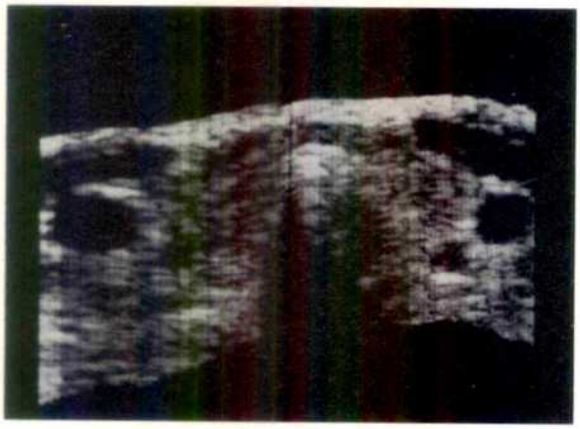


FIG. 3.

Rectilinear section scan of a normal thyroid taken through a water-bath (see text). Glandular tissue and surrounding anatomical landmarks are clearly visualized.

With the same geometrical configuration this type of scanner can be used in a time gated (or "constant depth") mode and an example of a scan of this type, taken of an excised human kidney is shown in Fig. 4. These two display modes, section and constant depth, are merely two-dimensional expressions of the basic three-dimensional data acquired by the scanner and, by appropriate digital techniques, such data can be stored and redisplayed in any aspect (Milan, 1972).

The rectilinear scanner is particularly well adapted to the examination of superficial organs and tissues but its use for deeper structures tends to be impeded by the presence of acoustic obstacles such as bone, occurring over its necessarily wide aperture of view. This restriction can be considerably eased, and the inconvenience of the water-bath normally eliminated while nevertheless retaining the feature of systematic scanning in three dimensions, if use is made of a scanning geometry in which the transducer face is constrained to a fixed position on the patient's skin and scanning movement of the beam is induced by appropriate manipulation of the back of the transducer. If, in particular, the scanning pattern is circular or spiral, mechanical movement will be smooth and potentially fast. With this type of "isocentric, skin-contact" movement (McCready and Hill, 1971a; 1971b) it is again possible to visualize a number of different scanning surfaces. Simple time

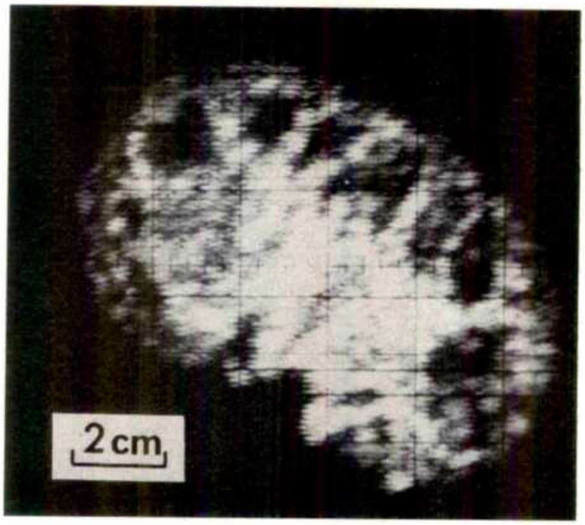
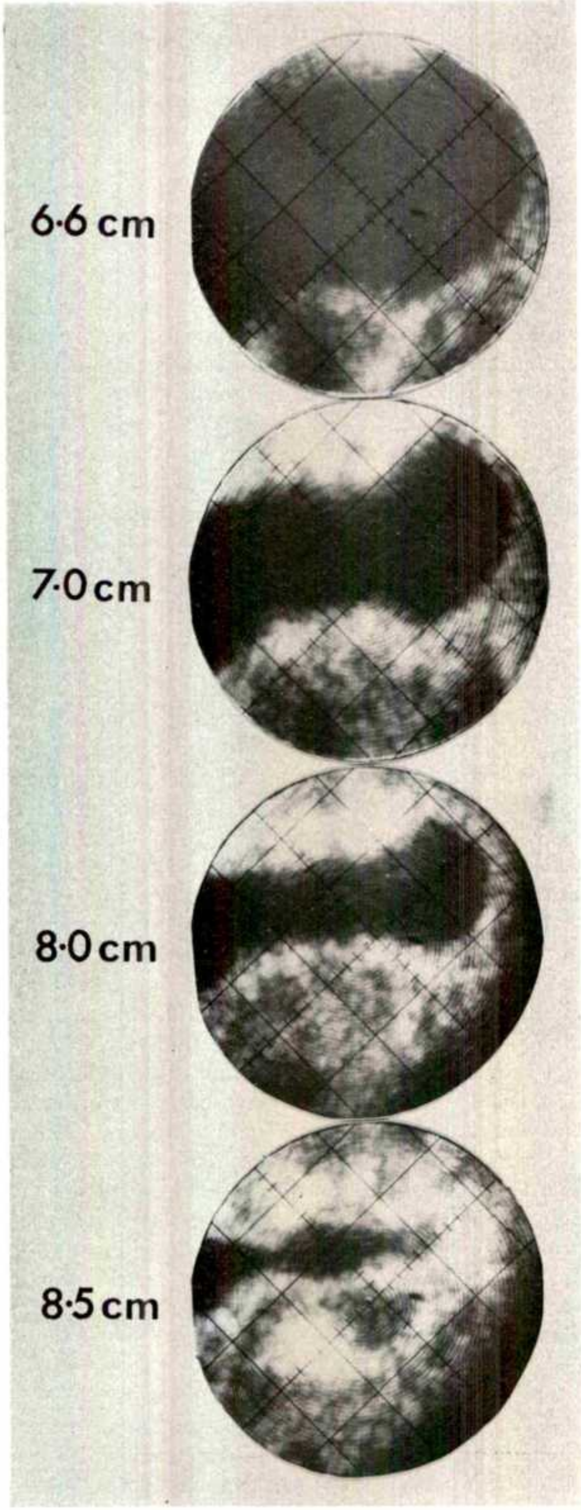


FIG. 4.

Rectilinear "constant depth" scan (time gated mode) of an excised human kidney.



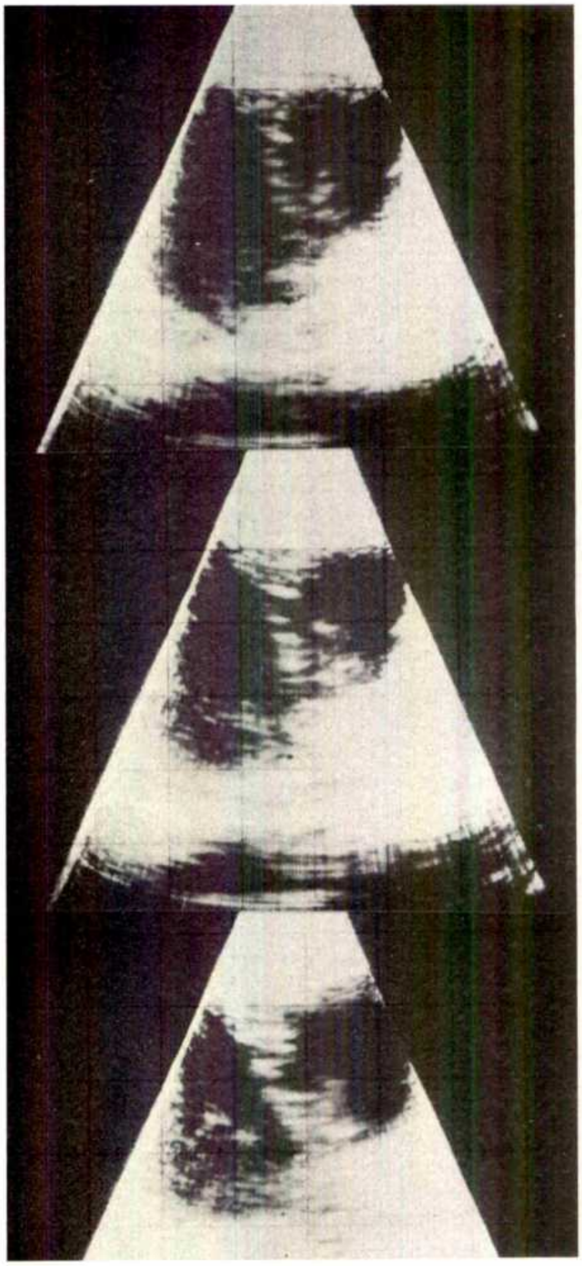


FIG. 6.

Conical section scans (Isocentric Spiral Scanner) of human heart at different phases of cardiac cycle. Time per frame: 20 ms; frame rate: 10 per second.

FIG. 5.

Isocentric spiral "constant depth" scans (corrected to plane geometry) of normal human bladder at four different depths in antero-posterior view.

gating defines a spherical surface centred at the transducer face but this may readily be modified to a plane surface by automatic adjustment of the gate position as the cone angle is varied. Alternatively the device can operate as a section scanner, either using the spiral motion or, more simply, by holding the cone angle constant and thereby generating a conical section scan. In this mode the high speed made possible by the smooth mechanical movement allows scans to be run fast enough to give essentially flicker-free visualization of moving structures such as the heart. Examples of the different types of scan obtainable with the isocentric scanner built for our system are shown in Figs. 5 and 6.

Signal Processing

Each scanner generates, and supplies to a common signal-processing unit, three sets of signals; a timing trigger (PRF), an r.f. echo signal and a pair of "X" and "Y" co-ordinate voltage signals. These signals constitute the basic data from which two- or three-dimensional visualization displays are derived and, although the principle of this derivation is conventional, our system includes a number of provisions designed to preserve the full information content of the incoming echo signals through to the final display. A small, low noise preamplifier is placed on the scanner, as close as possible to the transducer and electrically matched to it, in order to avoid unnecessary reduction in signal to noise ratio that would result from impedance loading and possible interference pickup in the 6 m of cable that is commonly necessary, between scanner and main amplifier, for flexibility in clinical work. Following time gain compensation (TGC) in the first stage of the main amplifier the maximum echo signals are about 60 dB above noise and, in order to preserve the signal information through to the display system, for which the maximum available dynamic range is about 20 dB, the second main amplifier stage is given a non-linear, three-stage compression response of the type described by Kossoff (1972). Operational experience has shown that the optimum compression characteristic may be different for different applications and an optional provision has therefore been made to by-pass one compression stage for applications, particularly in obstetrics and for radiotherapy planning, where a more "contrasty" image may be desirable. The output of the compression amplifier is detected and can be applied directly to brightness modulate the display, without filtering or suppression of low-level signals, both of which are processes that discard information but are nevertheless commonly used in order to produce pictures with a "clean" appearance. In order to ensure proper grey-scale representation it is essential that the time varying echo signal is applied to the brightness modulation circuit as an addition to a constant voltage pedestal ("unblank level" or "gate") which itself corresponds to the lower limit of the displayed grey-scale. In this condition even the smallest echo signals will produce a change in brightness level.

Time-gain compensation is applied in such a manner that amplifier gain increases linearly (in dB) with time, starting from a set time t_0, over a maximum range of 50 dB and with a slope whose value can be switched to correspond to the different transducer frequencies being used. When scanners are used in skin contact mode the starting time t_0 is derived as the time of arrival of the first echo (*i.e.* the skin echo), thus holding the gain at its minimum value over the lossless water path and activating both the gate and TGC at the point of entry into tissue.

Display and Recording

Desirable characteristics for a two-dimensional display and recording system have been discussed by Kossoff (1972) and include wide dynamic range and a spot size that remains small with brightness variation. The latter characteristic in particular is not shown by most general-purpose cathode-ray tubes, in which spot size tends to increase very considerably with brightness, while storage tubes have little or no dynamic range. We therefore use, for photographic recording of scans, a display oscilloscope that is specifically designed for brightness modulation (Tektronix type 604) and which is permanently coupled to a recording camera. Accurate and reproducible control of brightness level in this unit is important for good grey-scale performance and this is achieved by modifying the standard control to a dial indicating potentiometer. In order to be able to directly monitor the scans a second display unit, of the variable persistence storage type, is provided in parallel with the recording unit, while the corresponding A-scan and TGC characteristic are simultaneously displayed on the two channels of a small conventional oscilloscope.

Computer Compatibility

A system such as that described here can readily be made capable of providing information in a form that can be digitally coded and stored for subsequent analysis, processing and re-display (Milan, 1972). In our system, r.f. echo signals are taken to an analogue-to-digital converter (ADC) after time-gain compensation and a separate compression amplifier, designed to match the characteristics of the ADC, is included in the computer interface. The "X" and "Y" co-ordinate voltage signals are taken to the computer in parallel with the echoes but the PRF timing signals are, in this mode of operation, generated in the computer itself in order that synchronism can be maintained with the main computer timing system.

Acknowledgments

We are grateful to the Department of Health and Social Security for financial support and to numerous of our colleagues, particularly Drs. V. R. McCready and K. J. W. Taylor and Messrs. L. Jansson and J. V. Phelps, for help and advice.

REFERENCES

Hill, C. R., 1974. Interactions of ultrasound with tissues. In *Ultrasonics in Medicine*, pp. 14–20 (Excerpta Medica, Amsterdam).

Kossoff, G., 1972. Improved techniques in ultrasonic cross-sectional echography. *Ultrasonics*, *10*, 221–227.

Kossoff, G., Garrett, W. J., and Radovanovich, G., 1974. Grey-scale echography in obstetrics and gynaecology. *Australasian Radiology*, *18*(*1*), 62–111.

Lypacewicz, G., and Hill, C. R., 1974. Choice of standard target for medical pulse-echo equipment evaluation. *Ultrasound in Medicine and Biology*, *1*, 287–289.

McCready, V. R., and Hill, C. R., 1971a. A constant depth ultrasonic scanner, *British Journal of Radiology*, *44*, 747–750.

1971b. Ultrasonic scanning apparatus, U.K. Patent No. 8847/71.

Milan, J., 1972. An improved ultrasonic scanning system employing a small digital computer. *British Journal of Radiology*, *45*, 911–916.

Mountford, R. A., and Wells, P. N. T., 1972. Ultrasonic liver scanning: the A-scan in the normal and cirrhosis. *Physics in Medicine and Biology*, *17*, 261–269.

Taylor, K. J. W. and McCready, V. R., 1976. A clinical evaluation of grey-scale ultrasonography. *British Journal of Radiology 49*, 244–252.

Taylor, K. J. W., and Hill, C. R., 1975. Scanning techniques in grey-scale ultrasonography. *British Journal of Radiology*, *48*, 918–920.

Book review

Atlas of Lymphography. By T. De Roo, pp. 190, 387 illus., 1975 (The Netherlands, Leiden Stenfert Kroese bv), Dfl.85.

This atlas of lymphography contains a wide variation of illustrations of normal and abnormal lymphangiograms, and is the result of over ten years' personal experience in lymphography by Dr. Tom de Roo, in the Netherlands.

The history of the anatomists' discovery of the lymphatic system is beautifully presented, and ranges from Aristotle to Rouvière in 1932. The reproductions of the fifteenth-century drawings are fascinating.

There follows a good description of the anatomy and distribution of the vessels and nodes with diagrams from lymphograms. The terminology varies a little from the common English usage. We would term the para-lumbar nodes in the book para-aortic nodes and the para-aortic nodes pre-aortic nodes.

Techniques are bound to vary from one individual to another, but Dr. Roo's technique is well described. He uses specially adapted forceps to stabilize the lymph vessel and a spring-loaded cannula and stylet together with an injection pump.

Normal lymphograms are described and illustrated, and the films are all reproduced by logetronic prints, but unfortunately the very fine detail which is vital for interpretation is not always well seen. Differentiation is made between the appearances in acute and chronic infection of nodes. Whilst this is sometimes possible, the usual extreme difficulty in practice is not emphasized.

There is a commonsense approach to the scope of lymphangiography and the limitations of the examination in the near terminal case. Difficulties in interpretation are also discussed, but complications are stated to be only minor and thus dismissed. The importance of adequate respiratory function is not mentioned, and major complications are ignored.

The use of ancillary investigations such as inferior vena cava injections are well documented, and the tomograms reproduced are often vital to assess individual groups of nodes.

Beautiful illustrations of nodes involved in Whipple's disease, and in the more extensive infiltrations in Hodgkin's disease, lymphosarcoma and nodal metastases from various primary sites are also shown.

The atlas ends with illustrations of lymphatic vessel pathology including extravasation, and finally with an extensive reference section.

This book would be nice to have in a hospital library, or to own, if the reader is particularly interested in lymphangiography, but it is not comprehensive enough for a reference book, nor didactic enough about the parameters of normal for the uninitiated.

Audrey K. Tucker.

1976, *British Journal of Radiology*, *49*, 244–252

A clinical evaluation of grey-scale ultrasonography†

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(*Submitted March, 1975 and in revised form May, 1975*)

ABSTRACT

Recent technical improvements in grey-scale ultrasound imaging have resulted in the visualization of the internal consistency of soft tissues. This permits the diagnosis of diffuse pathology and detection of small space-occupying lesions. The new technique can be used with advantage in the currently accepted obstetrical applications for ultrasound imaging as well as for new non-obstetrical applications. The method has been found to be a most informative, non-intrusive means for investigating hepatobiliary disease and for the differential diagnosis of chronic splenomegaly.

The equipment described in the preceding paper (Hill and Carpenter, 1976) has been under active clinical evaluation during the past two years for the examination and diagnosis of some 4,000 patients. The work load has grown rapidly until at present the machine is used routinely on a wide variety of clinical problems. This has permitted an assessment of the clinical value of grey-scale imaging in addition to evaluating both the automatic scanning heads and manual scanning techniques.

An essential difference between conventional and grey-scale ultrasonography lies in the selective amplification and display of the low level echoes which are backscattered from interfaces within soft tissues. The amplitudes of these echoes are largely independent of the angle of incidence. This has two important implications: firstly, the advantage gained by compounding is reduced or eliminated; secondly, the data on echo amplitude are displayed in various shades of grey which depend primarily on the physical state of the tissue rather than the angle at which the beam is incident on the reflector.

Donald, McVicar and Brown (1958) introduced compounding as a scanning technique to improve the probability that, at least once during the course of a scan, the beam was at normal incidence to specular reflectors. The display of backscattered echoes on the other hand permits the use of a simple sector scan when examining the liver and kidney (Taylor and Hill, 1975). Simple linear scans were used by Kossoff (1972) for visualizing the breast. A major advantage of such simple techniques is that good resolution is maintained in spite of pulsation in the organ being examined. Each interface is recorded in a single position whereas, in a compounded scan, the interface moves during the scan and is registered in different positions.

The independence of the amplitude of the backscattered echo on the angle of incidence also raises the possibility that these amplitudes might yield diagnostically useful data on the physical state of the tissue. On theoretical grounds, Fields and Dunn (1973) proposed that an important site for echo production would be interfaces involving media of high bulk moduli. They noted that the supporting fibrous elements of tissue, such as collagen and elastin, have bulk moduli that may be several orders of magnitude greater than the other components of soft tissue. These therefore could be sites of echo formation. Mountford and Wells (1972a and 1972b) produced evidence which in retrospect appears to be consistent with this concept when they quantitated the echo amplitudes from cirrhotic and normal livers and found significantly higher levels in the cirrhotic livers. Taylor and Milan (unpublished work) made similar measurements on the spleen and found that the echo amplitude correlated with the degree of inflammatory change. Thus, for practical purposes, in the interpretation of a grey-scale ultrasonogram, the returned echo pattern can be considered to be a display of the fibrous supporting tissue. Space-occupying lesions are detected because they replace this normal structure.

At the present time, the manual sector scanner has been extensively evaluated on most softer organs. The automatic rectilinear scanner has been used through a water bath to scan superficial organs such as thyroid, testes and breast. These two techniques were found to be adequate for static imaging and superior to the spiral scanner in its present form. The spiral scanner is of some value in ophthalmic work although much higher frequencies can be used with advantage. It can also be used to image the heart in real time. However, the present system has geometical limitations and, in addition, organ movement has imposed limitations on the clinical value of constant depth scans produced by it.

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†Part of M.D. Thesis of K. J. W. Taylor, University of London, 1975.

MANUAL SECTOR SCANNING

Hepatobiliary disease

The grey-scale technique has been particularly useful in the diagnosis of hepatobiliary disease. Storage scope techniques permit successful differentiation of solid from cystic space-occupying lesions (Ostrum *et al.*, 1967). For example, ultrasound scanning has been especially valuable in the diagnosis of hepatic abscesses (Wang *et al.*, 1964; Butler and McCarthy, 1969).

In the diagnosis of metastatic disease of the liver, conventional (*i.e.* non-grey-scale) ultrasound is claimed to produce fewer false positives than isotope examinations (Gros *et al.*, 1972; McCarthy *et al.*, 1970). However, isotope examinations have been reported to be superior to ultrasound in detecting established metastatic disease. On the other hand, in patients with liver involvement which was clinically obvious, McCarthy *et al.* (1970) were unable to detect any abnormality in 53 per cent of the ultrasound scans, while Leyton *et al.* (1973) reported a failure rate of 39 per cent in a similar study.

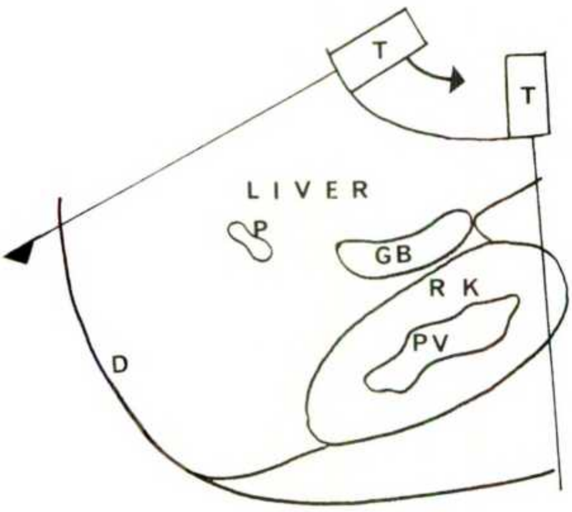

FIG. 1A.

Diagram to show movement of transducer (T) to produce parasagittal scan seen in Fig. 1B. P is the right branch of the portal vein, GB is the lumen of the gall-bladder, PV is the pelvi-calyceal system of the right kidney (RK) and D is the diaphragm.

These findings were probably due to inaccessibility of some parts of the liver and also to the inability to display the normal detailed anatomy. Using conventional machines, various patterns of echo complexes from metastases have been reported (Holmes, 1966; Holm, 1971; Melki, 1973). Using the grey-scale technique, the liver is seen as a uniform pattern of linear echoes with a constant pattern from small vessels. Metastases are usually seen as areas without vessels, of uneven structure and returning echoes of reduced amplitude. In a small percentage of patients, it is difficult to achieve an acoustic window to all or part of the liver due to air in the transverse colon. Bowel preparation may be required in such patients.

The liver is scanned by a series of parasagittal sections as shown schematically in Fig. 1A. The resulting ultrasonogram is shown in Fig. 1B. The liver is seen in longitudinal section, limited above by the right hemi-diaphragm. The lumen of the gall-bladder (GB) and the right kidney (RK) are clearly shown.

Multiple malignant tumours, seen as circular areas with reduced reflections, replace the normal liver substance in Fig. 2. Part of the right kidney is

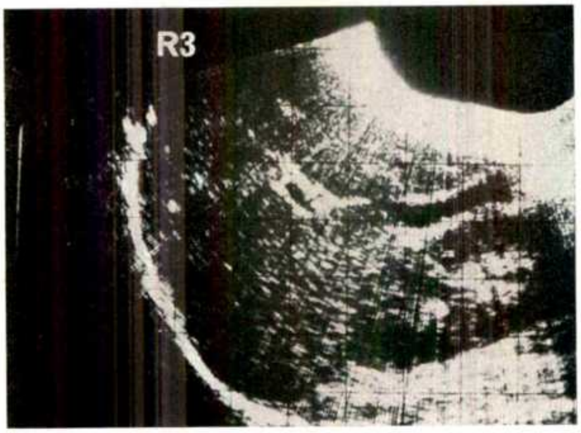

FIG. 1B.

Parasagittal scan showing the anatomy displayed in the schematic diagram.

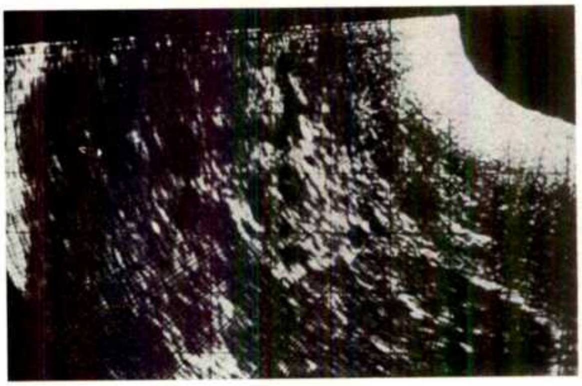

FIG. 2.

Parasagittal scan through liver and right kidney showing multiple small space-occupying lesions up to 2 cm diameter. Such highly homogenous tumours are seen in the lymphomas.

seen posteriorly. The grid lines are 2 cm apart so that the smallest detail successfully resolved is about 3 mm. However, it can be difficult to distinguish between a small tumour and blood vessel or bile duct. The appearance of the metastasis may give some indication of its origin (Taylor, 1974). Tumours that are acoustically homogeneous (black) as seen in Fig. 2, are most often due to lymphomas, Hodgkin's disease or colo-rectal primaries. With grey-scale echography, where small echoes are recorded, the differentiation between cysts, abscesses and necrotic tumours requires considerable experience. Benign cysts can usually be distinguished on the basis of their regular walls: the appearance of the A-scan, which shows a virtual absence of returned echoes, indicates little or no cellular debris within the cavity (Howry, 1965). Evidence of surrounding inflammatory changes supports the diagnosis of an abscess cavity.

One of the 17 abscesses examined is shown in Fig. 3. A multiloculated cavity can be seen (C) which returned very low-level echoes. There is evidently little attenuation within the lesion, since the more distal echoes have been overamplified by the time gain control (TGC or swept gain). These observations imply that the lesion is fluid filled and contains debris. However, the liver substance returns uneven high level echoes which are believed to be consistent with an inflammatory process. The appearances strongly suggest hydatid disease of the liver (unsuspected in this patient who had never been out of this country and was clinically remarkably well). The diagnosis was confirmed at laparotomy.

Diffuse liver disease can be diagnosed and benign changes differentiated from malignant ones. The appearances of fatty infiltration (confirmed histologically) are shown in Fig. 4 and are characterized by an even distribution of high-level echoes, frequently associated with dilated veins due to chronic venous congestion. These appearances have been seen in a number of patients who have presented with hepatomegaly and carcinoma of the bronchus. Although liver involvement is simulated on clinical examination, the characteristic ultrasound appearances permit the confident exclusion of malignant involvement.

The accuracy of the grey-scale technique in the diagnosis of hepatic disease has been reported by Taylor and Carpenter (1974a). In 120 patients coming to laparotomy or post mortem within three weeks of ultrasound scanning, the ultrasound interpretation was diagnostic in 82 per cent and contributed to the diagnosis in a further 10 per cent. The remaining 8 per cent were false positives or negatives. There is no doubt that the diagnostic accuracy increases with experience of using the technique.

During the period of clinical evaluation, some 70 patients were referred with carcinoma of the breast. Liver ultrasonography detected 14 out of 15 cases of liver involvement, for which it was more accurate

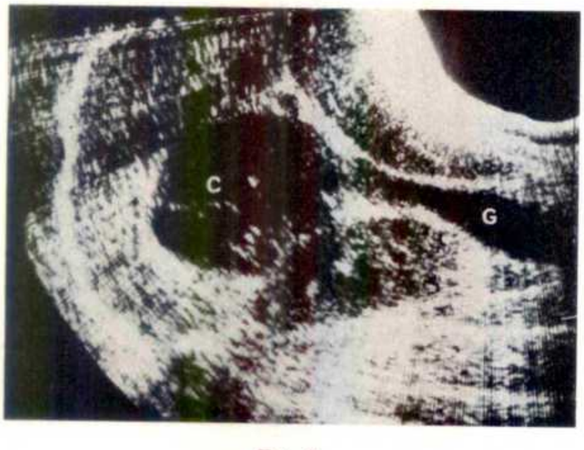

FIG. 3.

A large abscess cavity (C) can be seen replacing the liver parenchyma. The echoes beyond it are overcompensated for depth gain suggesting a fluid consistency. The liver substance returns uneven high-level echoes consistent with an inflammatory process. The gall-bladder lumen can be seen (G)

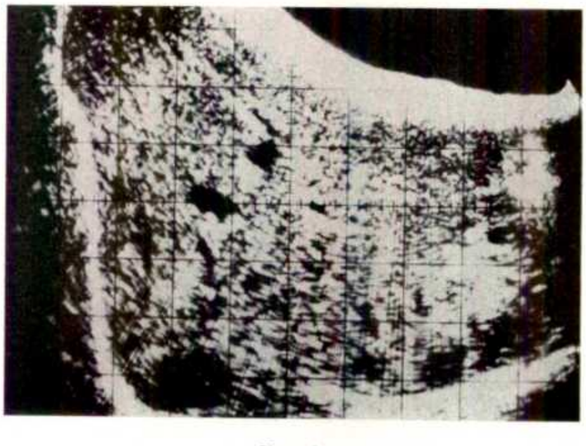

FIG. 4.

Parasagittal scan through liver and right kidney. The liver returns very high level echoes. These are interspersed by dilated vessels which are distributed in a characteristic pattern. These appearances are typical of fatty infiltration due to chronic venous congestion.

than clinical examination, isotope imaging or elevation of serum alkaline phosphatase. There were three false positive scans out of the remaining 55 cases (Smith *et al.*, 1975).

Ultrasound examination of the liver has become part of the routine work-up on patients with lymphomas and Hodgkin's disease. The method has most value in the advanced stages of these diseases in which liver involvement may occur. However, 50 patients came to a staging laparotomy and splenectomy soon after ultrasound examination and this permitted an accurate assessment of the accuracy of the method with reliable histological confirmation. The ultrasound results correctly predicted liver involvement in three out of five positive wedge biopsies while 42 out of 45 cases of non-involvement were correctly reported (Glees *et al.*, 1975).

Grey-scale ultrasonography has proven to be especially valuable in the non-invasive diagnosis of cholestatic jaundice (Taylor *et al.*, 1974; Taylor and Carpenter, 1974b). In 104 patients referred for investigation of cholestatic jaundice, differentiation between intra- and extrahepatic causes was correctly predicted in 97 per cent. Although the gall-bladder is frequently enlarged in extrahepatic biliary obstruction, it may not communicate with the rest of the biliary tree and should therefore not be used as the sole criterion of biliary obstruction. The biliary canaliculi can be visualized and can be seen to be abnormally distended (Fig. 5). In this particular figure, the gall-bladder can be seen and, although it is not abnormally large, it has a rounded distended appearance. With experience, these vessels can be distinguished from blood vessels but this requires a detailed knowledge of the anatomy of the vascular structures throughout the liver. The common bile duct may be visualized and the precise site of the obstruction determined, especially if care is taken to dispel air from the gut by appropriate preparation. During the last two years, 25 cases of carcinoma of the pancreas have been identified.

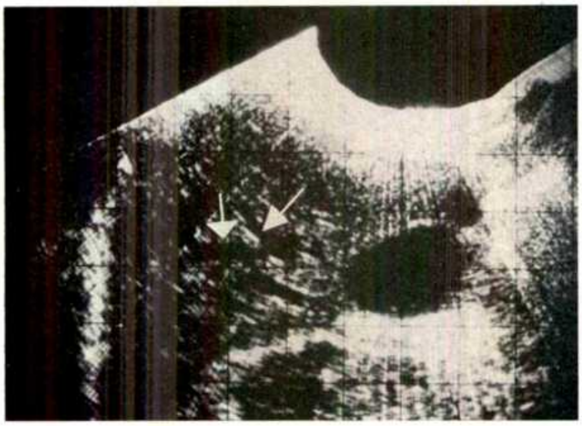

FIG. 5.

Parasagittal scan through liver and right kidney. The gall-bladder is distended but not abnormally large. There is definite dilatation of the intrahepatic biliary canaliculi (arrowed) which is diagnostic of extrahepatic biliary obstruction.

Spleen

Spleen size can be assessed using conventional ultrasonography (Holmes, 1972). To date, no diagnostic echo patterns have been described in association with any particular pathology (Barnett and Morley, 1974). The use of the grey-scale technique has permitted some attempts at the successful differential diagnosis of chronic splenomegaly based on the ultrasound pattern of the splenic consistency. In general, benign causes of chronic splenomegaly are characterized by the return of medium to high level echoes while malignant causes produce very low level echoes. At present, there is insufficient signal to noise ratio in this equipment to permit adequate differentiation between normal and malignant consistencies, and some further technical improvements are required in this and also in the direction of quantitative calibration of grey-scale values. Scans of benign and neoplastic spleens are compared in Figs. 6A and B. The large black spleen seen in Fig. 6A is from a patient with acute leukaemia. A definite pattern, rather like that shown by the placenta, is seen in Fig. 6B which is the spleen of a patient who was suspected of having a lymphoma; a benign cause was correctly predicted by the ultrasound result.

GENITO-URINARY SYSTEM

Kidneys

Our equipment has shown relatively little advantage over conventional techniques in the investigation of the urinary tract. This is probably not an inherent defect of the grey-scale imaging approach but stems from the current limitations of the equipment in respect to signal to noise ratio. The pelvicalyceal system is a strong reflector and is well visualized by current techniques (Barnett and Morley, 1974) whereas the cortex returns echoes of too low an amplitude to be registered. However, the use of simple sector scanning techniques permits dilation of the renal pelvis to be displayed (Taylor and Hill, 1975); this sign of minimal hydronephrosis has been observed even before the intravenous pyelogram became abnormal. Using conventional ultrasound equipment, some renal tumours may be

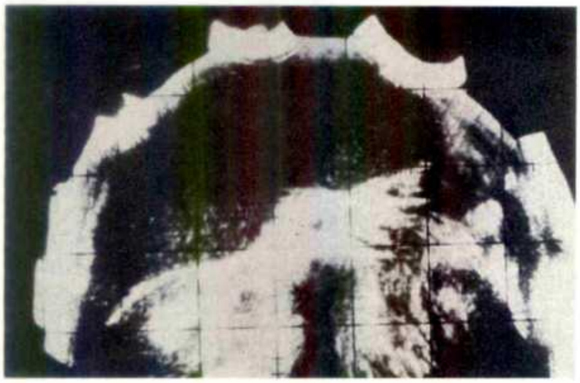

FIG. 6A.

Transverse scan of spleen in chronic lymphatic leukaemia. The spleen is virtually echo free although a few deep echoes may be displayed in patients who have been treated.

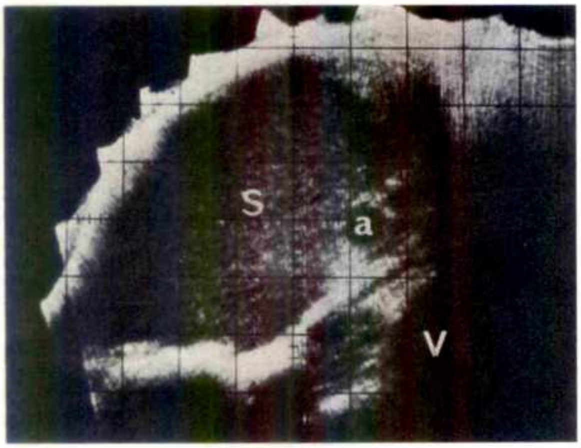

FIG. 6B.

Transverse scan of spleen (S) which returns a fine structure throughout. A splenic artery (a) can be seen. V is the vertebra. This is characteristic of benign splenomegaly.

misdiagnosed as cysts due to their extreme homogeneity. The grey-scale technique renders this less likely since low-level echoes are amplified and some internal structure is always observed in solid tumours. A Wilms tumour is shown in Fig. 7. It filled the left half of the abdomen in a two-year-old child. Although the upper pole of the tumour is highly homogeneous, there is a definite structure in most of the tumour material. As normally occurs in infants, the ultrasound beam has passed between the vertebrae.

Bladder

Again, the addition of grey-scale adds little to the data that may be obtained by conventional scanning (Barnett and Morley, 1971; 1972), and indeed, debris in the urine may be displayed to such an extent to interfere with the clinical value of the scan. However, the ability to register the whole range of echoes in a single scan implies that the bladder contents are displayed on the same scan which shows the degree of extravesical spread of a bladder tumour. A transverse scan of the bladder is shown in Fig. 8 with a tumour on the left posterior wall, and

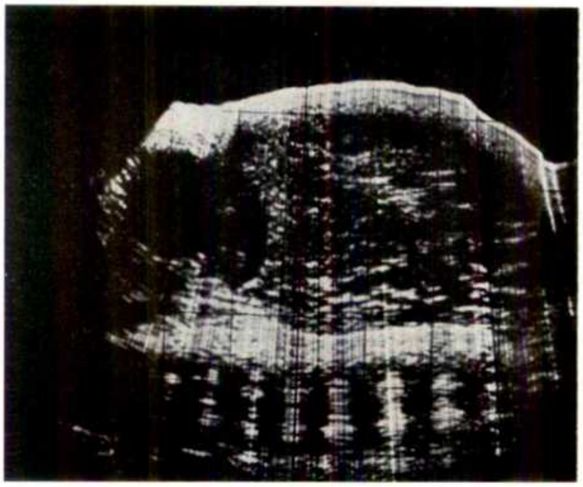

FIG. 7.

Parasagittal scan through the abdomen of two-year-old child. A large tumour mass with a homogeneous upper pole fills the abdomen. Posteriorly, the vertebral column is seen where the ultrasound beam has transversed the intervertebral discs.

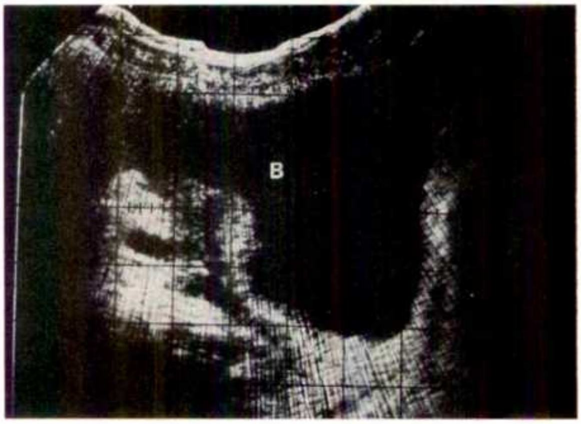

FIG. 8.

Transverse scan through bladder at level of symphysis pubis. The cavity (B) is the bladder contents and the lumen is encroached by a sessile tumour on the indurated posterior wall of the bladder. Homogenous tumour is seen spreading out from the base of the mass towards the left side of the pelvis.

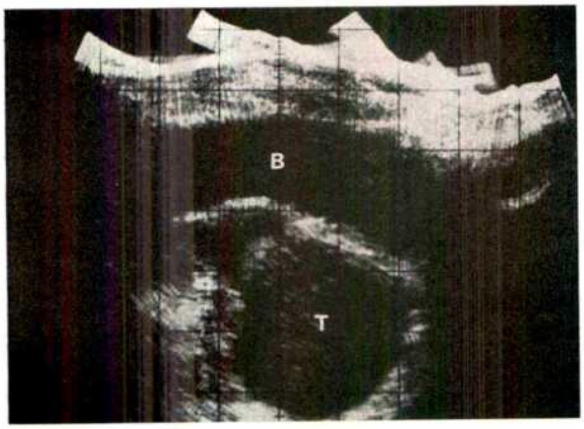

FIG. 9.
Transverse scan through bladder (B) at the level of the symphysis pubis. The posterior wall of the bladder is displaced forwards by a solid ovarian tumour (T) which proved to be a metastatic melanoma.

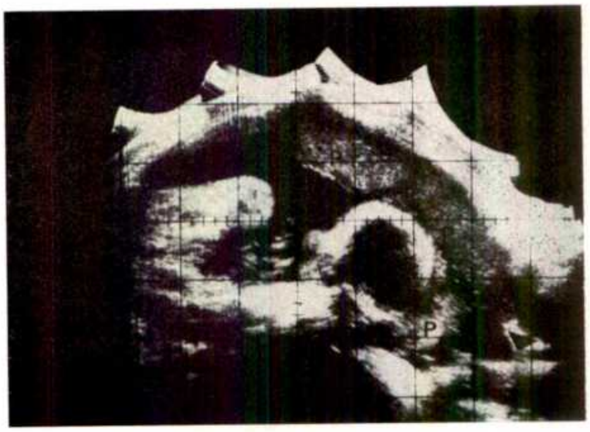

FIG. 10.
Longitudinal scan of gravid uterus showing fetus in vertex presentation. The placenta (P) has a definite structure to it and is seen anterior to the fetal head. It can be traced round the head onto the posterior wall of the uterus. The inferior edge of the placenta is irregular and there is probable haematoma between it and the internal os (arrowed).

neoplastic material spreading out into the left side of the pelvis. There is induration of the bladder wall which supported the conclusion that the tumour was malignant.

Ovary

Grey-scale techniques display solid tumour material and therefore it is easier to differentiate between solid and cystic ovarian masses; this is of particular value in the diagnosis of cystaden carcinoma of the ovary. An ovarian tumour, seen in Fig. 9, has a definite pattern throughout it. This patient was a 19-year-old female with widespread metastatic disease from a melanoma. Following the development of urinary incontinence only one physician out of four felt a pelvic mass in the patient. The ultrasound examination displayed the tumour clearly and the low-level echoes showed that it was solid rather than cystic.

Obstetrics

Conventional ultrasound permits highly accurate placental localization and determination of fetal maturity. For biparietal estimations, the conventional scan has a positive advantage since the contour of the head is displayed particularly clearly. However, the use of the grey-scale technique, which displays the substance of the placenta, makes placental localization more reliable even in less experienced hands. The detailed fetal anatomy which may be displayed by this technique has been strikingly shown by Kossoff and his colleagues (Kossoff, 1972; Kossoff and Garrett, 1972; Kossoff *et al.*, 1974). The technique therefore permits the *in utero* detection of congenital abnormalities. A gravid uterus is shown in Fig. 10 in which the fetal parts are well defined and the placental relation to the internal os can be assessed precisely.

RECTILINEAR SCANNER

Breast

Although ultrasound appears to be an attractive alternative to ionising radiation for the detection of lumps in the breast, a tomographic technique is unsuited to the mass screening of healthy patients. The 100–200 sections required per patient would pose practical difficulties in execution and interpretation. Grey-scale ultrasonography has been used successfully to differentiate adenomas, cysts and carcinomas (Kosoff, 1974). However, in the practical management of a patient, a breast lump is nearly always excised or aspirated, enabling the nature of the mass to be established definitively. Ultrasound imaging may be of value as a radiation-free technique to follow-up lumps which have not been excised.

Thyroid

Grey-scale ultrasonography has been successfully used in the examination of the thyroid to differentiate cold areas on the isotope scan due to adenomas, cysts and malignancies (Taylor and McCready, 1975). The display of normal glandular tissue is essential for the reliable differentiation of benign and malignant masses of the thyroid. Malignant tissue in the thyroid is characterized by returning echoes of lower amplitude than those from normal tissue (Crocker *et al.*, 1974). Adenomas usually are seen as circumscribed areas with high level echoes. Fluid-containing areas produce no echoes while a typical scan showing a cyst involving the anterior aspect of the left lobe is seen in Fig. 11.

Testis

Testicular scanning has been reported using conventional ultrasound equipment (Miskin and Bain, 1974) but the inability to define the normal consistency of the organ precludes recognition of any small impalpable tumour. The rectilinear scanner, together with a grey-scale technique, enables small tumours and other lesions to be seen. A small tumour in the left testis of a patient who presented with a mediastinal teratoma is shown in Fig. 12. The clinical problem in the management of this patient was to establish whether the mediastinum was the primary site of the tumour or whether this was metastatic from an occult tumour in the testis. The ultrasonogram shows a small defect in the edge of the left testis, which solved this problem.

DISCUSSION

The recent availability of grey-scale high resolution ultrasonography has greatly improved the diagnostic capabilities of this technique. The results presented indicate our preliminary assessment of where such techniques are useful in clinical diagnosis. However, in such a short time only relatively little experience has been gathered and it is obvious both that the diagnostic accuracy will improve further and that the range of worthwhile applications for both the manual and automatic scanning techniques will increase.

The initial interest and concentration on automatic scanning techniques has been overshadowed by the quality and diagnostic value of the manual grey-scale sector scans. The speed with which the results have become useful clinically has resulted in little time being left to fully assess the automatic scanning methods. Nevertheless the constant depth and spiral scans have not realized their initial promise. Automatic rectilinear scans of the thyroid are likely to be especially useful as a complementary investigation to the isotope scan. The rectilinear breast scans show promise but with the quality attainable with mammograms and xeroradiography it seems that our limited resources should be concentrated on the other soft tissues where alternative investigations are poor or absent.

The outstanding improvements in diagnosis have been in the area of liver disease. Here, fine detailed anatomy is visible throughout the liver so that vessels and other structures as small as 3 mm diameter can be seen, making the diagnosis of early metastases and other space occupying lesions possible. The ability to see small biliary ducts is especially useful in the investigation of cholestatic jaundice where ultrasound fills a previous hiatus in our diagnostic capability.

The fine anatomy displayed by this technique, requires for successful interpretation, a detailed knowledge of the anatomy and pathology of the

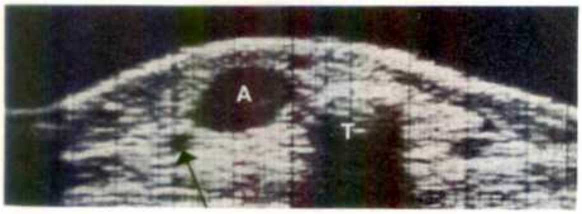

FIG. 11.

Transverse scan of thyroid. The trachea appears black (T) and the lateral lobes of the thyroid lie on either side of it. There is a 2 cm cyst (A) in the left lateral lobe. The common carotid artery (arrowed) is just resolved.

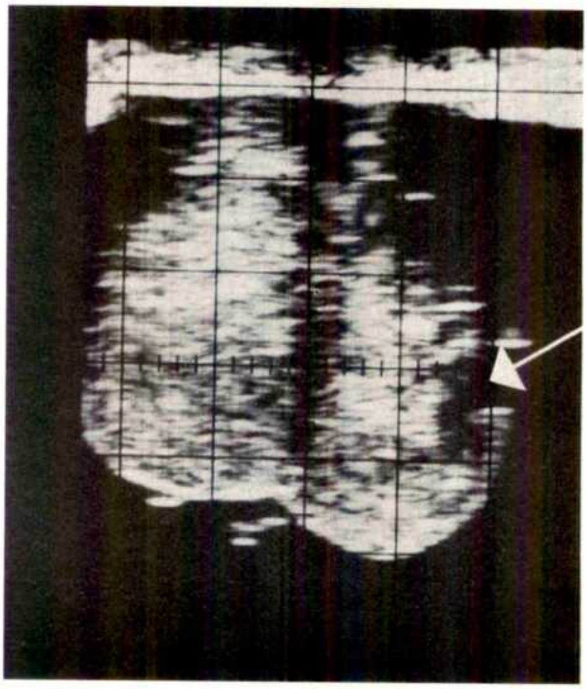

FIG. 12.

Transverse scan both testes. There is a small defect due to an occult tumour (arrowed) in the margin of the left testis.

liver as revealed by grey-scale ultrasonography. The diagnosis of necrotic tumour, cysts and abscesses requires attention to features such as the number present, the shape of the lesion and its internal structure. Thus, although considerable experience is required to make a confident diagnosis, the method is potentially so accurate that time spent in training is worthwhile.

The spleen is an organ which has proved difficult to assess by plain radiography or isotope methods. Our preliminary work would indicate already that ultrasound grey-scale techniques will be of great value even in diffuse diseases. Very encouraging results have been found in the genitourinary system although grey-scale techniques have less advantage over conventional scanners. However, the high resolution and intratumour details visualized indicate that better equipment yields better quality pictures even if the overall diagnostic accuracy is not markedly improved.

Of course conventional techniques have been highly successful in the obstetrics field for many years. The grey-scale technique makes placental identification considerably easier even in less experienced hands. In this field the quality of the scans obtained by Kossoff and his team, using grey scale coupled to an automatic scanner, would suggest that future departments are likely to have a series of specialized ultrasound scanners for specific organs.

In some applications, ultrasound techniques may replace current intrusive imaging techniques but in general they offer extra information which complements other diagnostic techniques.

ACKNOWLEDGMENT

We wish to acknowledge financial support by the Department of Health and Social Security for the development of the instrumentation used in this study.

REFERENCES

Barnett, E., and Morley, P., 1971. Ultrasound in the investigation of space-occupying lesion of the urinary tract. *British Journal of Radiology*, *44*, 733–742.

1972. Diagnostic ultrasound in renal disease. *British Medical Bulletin*, *28*, 196–199.

1974. Urinary tract. In *Abdominal Echography-Ultrasound in the Diagnosis of Abdominal Conditions*, pp. 53–69 (Butterworths, London).

Butler, T. J., and McCarthy, C. F., 1969. Pyogenic liver abscess. *Gut*, *10*, 389–399.

Crocker, E. F.McLaughlin, A. F., Kossoff, G., and Jellins, J., 1974. The grey-scale echographic appearances of thyroid malignancy. *Journal of Clinical Ultrasound*, *2*, 305–306.

Donald, I., McVicar, J., and Brown, T. G., 1958. Investigation of abdominal masses by pulsed ultrasound. *Lancet*, *1*, 1188–1194.

Fields, S., and Dunn, F., 1973. Correlation of echographic visualizability of tissue with biological composition and physiological state. *Journal Acoustic Society of America*, *54*, 809–812.

Glees, J., Taylor, K. J. W., Gazet, J. C., and Peckham M. J., 1975. Superior accuracy of grey-scale ultrasonography of liver and spleen in Hodgkin's disease and lymphomas compared with isotope scans. *Clinical Radiology* (in press).

Gros, C., Walter, J. P., and Parisot, B., 1972. Echography in liver pathology. *Journal de Radiologie d'electrologie*, *53*, 740–741.

Hill, C. R., and Carpenter, D. A., 1976. Ultrasonic Echo imaging of tissue: Instrumentation. *British Journal of Radiology 49*, 238–243.

Holm, H. H., 1971. Ultrasonic scanning in the diagnosis of space-occupying lesions of the upper abdomen. *British Journal of Radiology*, *44*, 24–36.

Holmes, J. H., 1966. Ultrasonic diagnosis of liver disease. In *Diagnostic Ultrasound*, eds. C. C. Grossman, J. H. Holmes, C. Joyner and E. W. Purnell, pp. 249–265 (Plenum Press, New York).

1972. *Ultrasonic studies of the abdomen*, p. 61 (Colorado; University of Colorado School of Medicine).

Howry, D. H., 1965. A brief atlas of diagnostic ultrasonic radiologic results. *Radiologic Clinics of North America*, *3*, 433–452.

Kossoff, G., 1972. Improved techniques in ultrasonic cross-sectional echography. *Ultrasonics*, *10*, 221–229.

1974. Display techniques in ultrasound pulse echo investigations: A review. *Journal of Clinical Ultrasound*, *2*, 61–72.

Kossoff, G., and Garrett, W. J., 1972. Ultrasonic film echography in gynecology and obstetrics. *Obstetrics and Gynecology*, *40*, 299–305.

Kossoff, G., Garrett, W. J., and Radavanovich, G., 1974. Ultrasonic atlas of normal brain of infant. *Ultrasound in Medicine and Biology*, *1*, 259–266.

Leyton, B., Halpern, S., Leopold, G., and Hagen, S., 1973. Correlation of ultrasound and colloid scintiscan studies of the normal and diseased liver. *Journal of Nuclear Medicine*, *14*, 27–33.

McCarthy, C. F., Davies, E. R., Wells, P. N. T., Ross, F. G. M., Follet, D. H., Muir, K. M., and Read, A. E. A., 1970. A comparison of ultrasonic and isotopic scanning in the diagnosis of liver disease. *British Journal of Radiology*, *43*, 100–109.

Melki, G., 1973. Ultrasonic patterns of tumours of the liver. *Journal of Clinical Ultrasound*, *1*, 306–314.

Miskin, M., and Bain, J., 1974. B mode ultrasonic examination of the testis. *Journal of Clinical Ultrasound*, *2*, 307–311.

Mountford, R. A., and Wells, P. N. T., 1972a. Ultrasonic liver scanning: the quantitative analysis of the normal A scan. *Physics in Medicine and Biology*, *17*, 14–25.

1972b. Ultrasonic liver scanning: The A scan in the normal and in cirrhotics. *Physics in Medicine and biology* *17*, 261–269.

Ostrum, B. J., Goldberg, B. B., and Isard, H. J., 1967. A mode ultrasound differentiation of soft tissue masses. *Radiology*, *88*, 745–749.

Smith, I., Taylor, K. J. W., McCready, V. R., and Powles, T., 1976. Comparison of grey-scale ultrasound with other methods for detection of liver metastases from carcinoma of breast (Submitted for publication).

Taylor, K. J. W., 1974. Letter. *Journal of Clinical Ultrasound*, *2*, 74–76.

Taylor, K. J. W., and Carpenter, D. A., 1974a. Comparison of radioisotope and ultrasound examination in the investigation of hepatobiliary disease. In *Ultrasound in Medicine*, Vol. 1. Ed. D. White, pp. 159–167 (Plenum Press, New York).

1974b. Grey-scale ultrasonography in the investigation of obstructive jaundice. *Lancet*, *11*, 586–7.

Taylor, K. J. W., Carpenter, D. A., and McCready, V. R., 1974. Ultrasound and scintigraphy in the differential diagnosis of obstructive jaundice. *Journal of Clinical Ultrasound*, *2*, 105–116.

TAYLOR, K. J. W., and HILL, C. R., 1975. Scanning techniques in grey-scale ultrasonography. *British Journal of Radiology*, *48*, 918–920.

TAYLOR, K. J. W., and MCCREADY, V. R., 1975. Comparison of radioisotope and ultrasound scans of the thyroid. *Proceedings of the Royal Society of Medicine*, *68*, 381–384.

WANG, H. F., WANG, C. E., CHANG, C. F., KAO, J. Y., YU, L., and CHIANG, Y. N., 1964. The application and value of ultrasonic diagnosis of liver abscess; a report of 218 cases. *Chinese Medical Journal*, *83*, 133–140.

Book review

Brain Scintigraphy. By Lourens Penning and Dov Front, pp. xi+384, 1975 (Amsterdam, Excerpta Medica), Dfl. 148.00.

There is one strange thing about this excellent book. Apart from their names, it is difficult to discover any information about the authors. Both will be known to all of us who are interested in cerebral scanning from their published works. Professor Penning is a neuroradiologist at the University Hospital of Groningen, and Professor Front is a neurologist working in the Nuclear Medicine Department of the University of Haifa. That both authors are very clinically orientated is one of the chief delights of this book. Indeed, the title is misleading, for this is far more than a text-book of brain scintigraphy.

The book is divided into sections, and each section is sub-divided into the written text and the illustrations. This subdivision can be disturbing to one's concentration, requiring a search some 10 to 20 pages farther on for the correct illustration. Even with this arrangement there is a considerable amount of empty space between the illustrations which could have been used to increase the size of the robot pictures which are rather small for those not used to this technique. However, these are minor criticisms, and considering the profusion of pictures, the layout and format may have been inevitable. The quality of the pictures is superb, and a nice mixture of other neuroradiological techniques is included.

The first section of the book deals with the normal scintigram, technique and normal anatomical details. The technique adopted is exhaustive, and one doubts if it could be practised in many departments in the United Kingdom. Rapid sequential pictures up to three per second are taken by Robot 35 mm camera and followed by Polaroid film every 20 seconds, and at increasing intervals up to 30 minutes. Static scans are taken at one hour and may be repeated at three hours. This data may be increased in certain cases by an intra-arterial injection of isotope. Obviously, such a technique requires at least one gamma-camera dedicated totally to neuroradiology. There is, however, no doubt that this technique yields a lot of information in the author's hands.

The second section deals with the abnormal scintigram. It contains a whole mine of information about cerebral tumours, infection, trauma, vascular lesions and a lot of other conditions—clearly presented and with excellent illustrations. The value of dynamic and sequential studies in the differential diagnosis of tumour histology is well discussed.

The third section deals with CSF flow studied by cisternography—the problems of normal pressure hydrocephalus, of CSF leaks and various cystic conditions are all dealt with and the authors' considerable experience in this still developing area is again illustrated well and supported by line-drawings.

The book, as a whole, gives a comprehensive and detailed account of cerebral scintigraphy including isotope arteriography, sequential and late static studies. There is an extensive list of references. It is well produced and a credit to the publishers—it even remains open at any chosen page. The price is high—approximately £30. Nevertheless, even if this sum is beyond the pocket of some individuals, this book is a must for every department of neuroradiology and of nuclear medicine.

A. S. BLIGH.

1976, *British Journal of Radiology*, *49*, 253–261 MARCH 1976

Radiation exposure to the patient in xeroradiography

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(*Received July, 1975*)

ABSTRACT

The paper presents measurements of the radiation exposure required in xeroradiography of the breast and of the extremities. The nature of the radiation hazard and the most appropriate quantity by which to assess it are discussed, and it is shown that for a number of radiological procedures xeroradiographs can be taken for about the same radiation exposure to the patient as that required by conventional film techniques.

The increasing use of xeroradiography for mammography has stimulated interest in other applications of the same method, and has made it necessary to examine in some detail the radiation exposure which this technique requires.

In the present paper the special field of mammography is examined first and then, for a series of other radiological procedures, the skin exposure incurred for xeroradiography is compared with that for a conventional film-screen combination.

The sensitivity of the recording medium is not the only factor influencing patient exposure. The optimum X-ray tube settings are different for the two recording media, and there are other technical matters, *e.g.*, whether an anti-scatter grid can be dispensed with, which complicate the comparison.

Several reports of patient dosage in xeromammography have appeared in which the comparison between this and other techniques has been made solely on the basis of a measurement of exposure at the skin surface. We discuss below whether this is the best criterion for assessing the small hazard involved.

MEASUREMENT OF EXPOSURE

Throughout this paper the quantity measured and tabulated as an assessment of risk to the patient is the *exposure*† in röntgens. This quantity can be quoted without ambiguity, whereas the absorbed dose in rads depends markedly on the atomic composition of the irradiated tissue, and may be appreciably higher in the skin (due to the sulphur contained in keratin) than in muscle or fatty tissue in the same low voltage X-ray beam at the same depth (Gray, 1940). It is frequently far from clear what conversion factor has been used by an author in deriving "absorbed dose in skin", and as our measurements (and those of most other workers) have been made with instruments calibrated ultimately against a free-air chamber, we believe the likelihood of error will be reduced if the basic exposure measurements are quoted. Absorbed dose in different types of tissue can be calculated from these.

Our measurements were made with an EIL portable electrometer Type 37C‡ using the 35 ml. ionization chamber. This was calibrated against a secondary standard instrument, itself calibrated at the National Physical Laboratory, over an appropriate range of photon energies. Thermoluminescent detectors in the form of LiF in Teflon discs were also used for measurements through a breast phantom, and LiF rods for assessing incident and exit skin exposure values over a patient's breast. These were calibrated by us against the ionization chamber, but no correction has been made for any variation in sensitivity due to the changing quality of the beam with depth in tissue. In the later stages of the work, an Ardran-Crooks cassette calibrated at the National Physical Laboratory was used to determine the effective X-ray tube voltage. Exposure measurements were made in several centres with the cooperation of the radiologists involved.§

MAMMOGRAPHY

Nature of the hazard

In mammography, the gonad dose should be entirely negligible, since the soft radiation used can easily be screened from the lower trunk. There is, therefore, no genetic hazard to the population to be considered, but only the somatic hazard to the patient herself. In any patient who presents with suspicious symptoms, the immediate need for the best possible radiographic examination is so much more important than the very slight risk of fresh tumour induction that a comparison of techniques on a basis of small dosage differences seems irrelevant. The technique which best serves the patient's interest is the one which in the opinion of the radiologist gives the best chance of detecting any malignant lesion and of defining its extent. It is only if mammography is to be employed widely as a regularly-repeated screening test for women with no clinical symptoms, that the small carcinogenic hazard must be weighed carefully against the chance of detecting an early malignant tumour not yet showing any other signs—this being also a relatively small chance. Several screen-film combinations have recently been introduced which allow a mammogram to be taken with a skin exposure of less than 0·5 R.

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†This can be converted to the newer SI quantity "kerma in air" expressed in Joule/kg by multiplying by the factor $8{\cdot}69 \times 10^{-3}$.

‡Made by Electronic Instruments Ltd.

§See Acknowledgments.

If a general screening programme by mammography should ultimately be shown to be effective in reducing mortality, and to be feasible economically, it is to these, or other, more sensitive recording techniques that one must turn. For use on patients with suspected lesions, however, the diagnostic quality of the picture is the primary criterion, and even in a screening programme this is the fact which will determine the number of early tumours detected and so it must be given due weight alongside the dosage comparison.

In mammography, very little bone marrow is irradiated. The tissue at risk for carcinogenesis is almost entirely the soft tissue of the breast itself and that surrounding the axillary nodes. There is no evidence to suggest that skin is any more liable to tumour induction than the underlying connective tissue, and so the total energy absorbed in the soft tissues would seem to be a more appropriate criterion of risk than the skin exposure.

This quantity can be derived, with an accuracy adequate for protection calculations, from a measurement of skin exposure (röntgens) and a knowledge of the X-ray beam quality. We do this in a later paragraph for a variety of irradiation régimes used in mammography.

Choice of irradiation régime for mammography

The parameters available for choice are:

(1) focus-skin distance (FSD);
(2) tube kV;
(3) anode material and filtration.

(1) A long FSD will reduce patient exposure slightly, but not dramatically. It requires a more powerful X-ray set, and manufacturers of mammographic equipment have generally chosen a fixed FSD less than 50 cm. Increasing this to 100 cm would reduce skin exposure to a 4 cm thick breast by less than 10 per cent. The longer FSD may, however, give better resolution due to the smaller effective focal spot size.

(2) With xeroradiography it is possible to use higher voltage X-ray beams than would yield acceptable results with film. The sensitivity of the selenium plates, expressed in terms of "reciprocal rontgens",* increases with increasing tube kV over the range used in mammography and the edge contrast development method prevents any significant loss of diagnostic information. To obtain adequate contrast in film mammography it is usual to choose a tube voltage of about 30 kV.

(3) If a tungsten anode is chosen, any soft L-radiation not absorbed in the tube window would contribute to surface dose without making any significant contribution to picture formation and must therefore be filtered out: 0·5 mm of aluminium achieves this adequately. With a molybdenum anode most of the energy is in the two groups of characteristic lines near 17·5 keV and 20 keV. The continuous spectrum above 20 keV can be greatly reduced with little effect on the line spectrum by using a 0·03 mm thick filter of molybdenum. The principal effect of increasing the kV on a Mo-anode tube filtered in this way is to enhance the output of characteristic radiation, but it also brings back some of the more penetrating continuous spectrum.

Marshall *et al.* (1975) have recently published a survey of diagnostic X-ray spectra measured with a Li-drifted germanium crystal, and have calculated the effect of different filters by an appropriate computer program. They kindly used their data and computer programs to plot the spectra from the two mammography régimes discussed below, and these spectra are reproduced in Fig. 1 (Marshall and Peaple, 1974).

The two régimes chosen for comparison were:

(a) a tungsten anode tube with 0·5 mm Al filtration used at long FSD (82 cm) to reduce skin exposure to a minimum;
(b) a molybdenum anode tube with 0·03 mm Mo filter at 38 cm FSD in the Siemens "Mammomat".

Incident skin exposure, depth dose and energy fluence per röntgen.

The skin exposure in the above two régimes for a range of tube kilovoltage and milliampere-seconds (mAs) was measured by the EIL ionization chamber. It was found to increase by a power law with kV and linearly with mAs thus allowing us to construct a simple chart giving skin exposure as a function of kV and mAs for each régime. These charts

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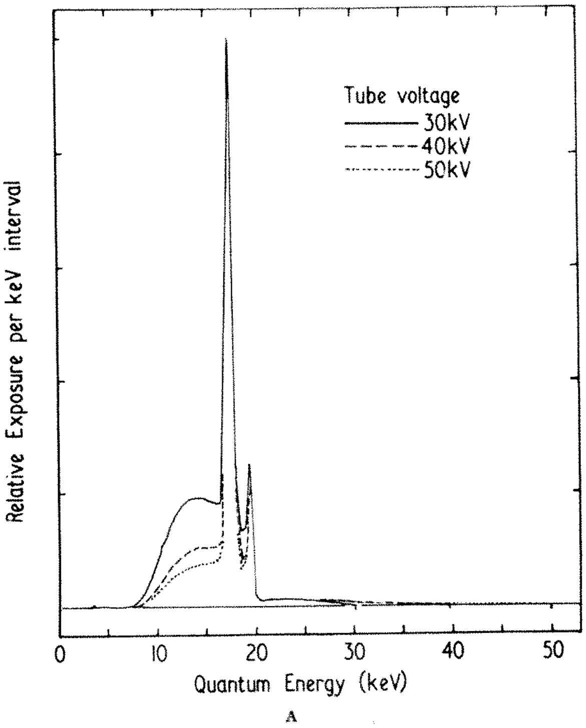
* *i.e.*, the reciprocal of the exposure needed to half discharge the selenium plate (see Boag, 1973).



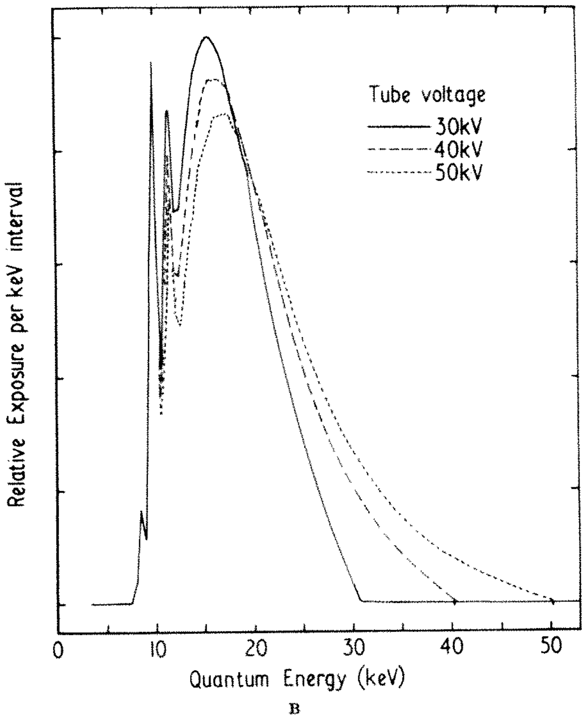


FIG. 1.

Spectral distribution of the radiation from (A) a Mo-anode tube with 0·03 mm Mo filter excited at 30, 40 or 50 kV and (B) a W-anode tube filtered by 0·5 mm of Al and excited at 30, 40 or 50 kV. The spectra have been normalized to the same peak height of the principal line, to demonstrate changes in shape. (Measurements and calculations by Marshall and Peaple, 1974.)

are reproduced in Figs. 2A and 2B. Similar charts can be constructed for any other irradiation régime.

The central axis depth exposure curves for these two régimes at several tube voltages are presented for fat-equivalent material in Fig. 3 and for muscle-equivalent material in Fig. 4. Most of the filtered output of the Mo-anode tube being concentrated in the characteristic lines at 17·5 keV and 20 keV, the depth exposure curves for this tube at both 30 kV and 50 kV exciting voltage lie far below those for the tungsten tube at these same voltages. The greater FSD of the latter tube makes a small contribution, of course, to this difference.

A breast of average size, pressed flat for mammography, yields a tissue thickness of some 4–5 cm. Very small breasts may compress to 2 cm, and large ones remain more than 6 cm thick. Figure 4 shows that the beam from a Mo-anode tube is almost completely absorbed in the average breast: the exposure rate is down to some 13 to 18 per cent at a depth of 4 cm in fat and to less than 5 per cent in 4 cm of muscle. Even for only 2 cm thickness of tissue the incident exposure rate is reduced to between 40 per cent (fat) and 10 per cent (muscle) at exit. For the estimation of the carcinogenic hazard we shall not be far out if we assume that the whole energy of the Mo-anode X-ray beam is absorbed in the breast tissue. In Table I the calculated fractions for a 4 cm breast range from 0·93 to 0·97.

Even in the case of the more penetrating radiation from the tungsten anode tube, 4 cm of fat reduced the exposure rate to less than 40 per cent of the incident value and 4 cm of muscle to less than 20 per cent. For a 4 cm breast the absorption fractions in Table I range from 0·72 at 50 kV to 0·82 at 30 kV.

The energy fluence per röntgen in a monochromatic X-ray beam is inversely proportional to the energy absorption coefficient, μ_{en}, of air, which falls rapidly as the quantum energy increases from 15 keV up to 100 keV, *i.e.*, throughout the diagnostic energy range. The rising curve of energy fluence per röntgen for a monochromatic beam is shown in Fig. 5 and from this it is clear that 1 R of X-radiation generated at 50 kV on a tungsten target tube (mean

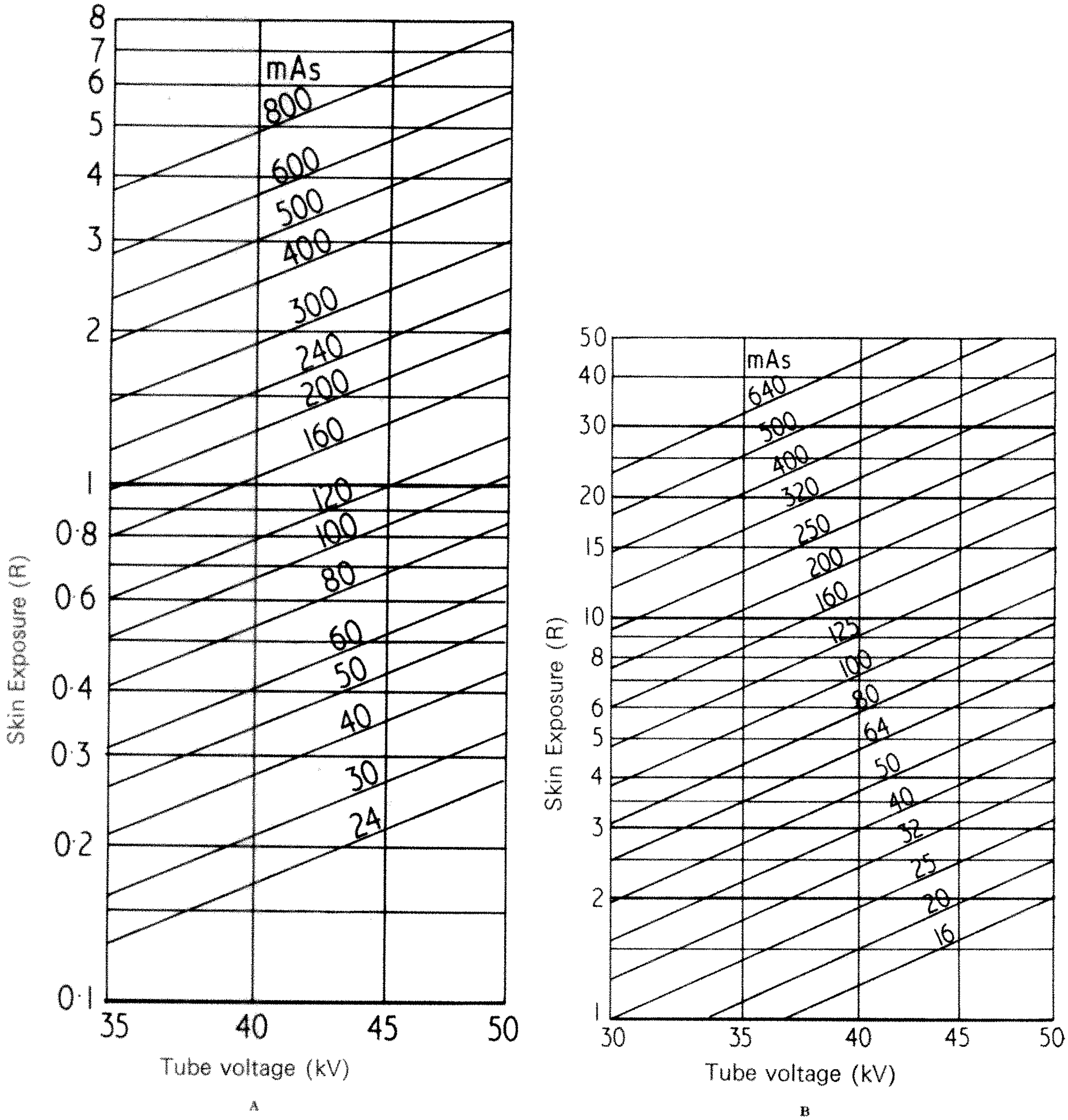


FIG. 2.

Skin exposure (including 10 per cent backscatter) as a function of kV and mAs for (A) a Mo-anode tube at 38 cm FSD with 0·03 mm Mo Filter (Mammomat), and (B) a W-anode tube at 82 cm FSD with 0·5 mm Al filter (Machlett).

quantum energy approx. 27 keV) carries considerably more energy into the breast than 1 R of the characteristic radiation from a molybdenum target tube (quantum energy 17·5 and 20 keV).

Using the spectral distribution provided by Marshall and Peaple (1974) (Fig. 1), we have calculated the energy fluence per röntgen for each of our two régimes, and give these in Table I. In the final column of that table we calculate the energy retained in a 4 cm thick breast per R incident, assuming that the absorption fractions are those calculated and set out in another column of the same table.

Xeromammography compared with non-screen film

Table II presents data compiled during some two

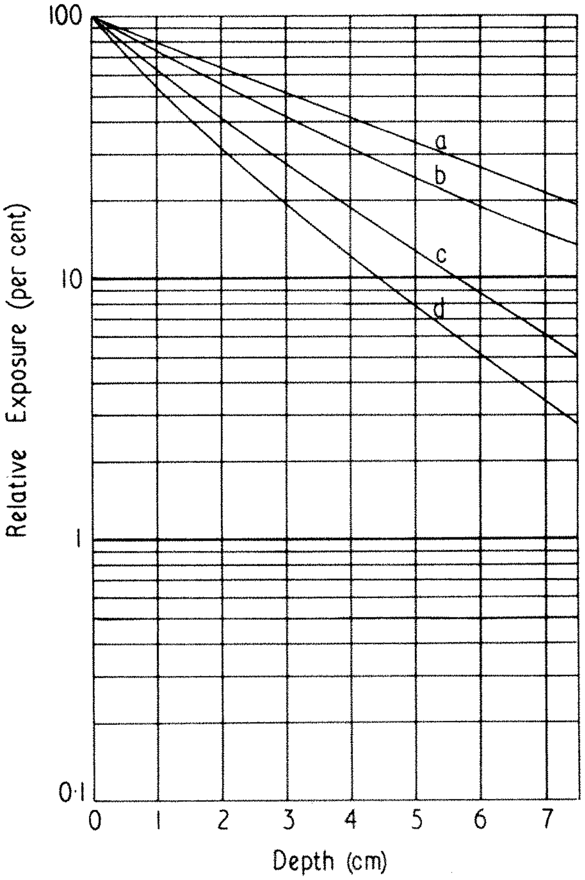


FIG. 3.

Variation of exposure through fat-equivalent material for the two X-ray régimes represented in Fig. 2.

(a) W-anode	50 kV tube potential	82 cm FSD
(b) W-anode	30 kV tube potential	
(c) Mo-anode	50 kV tube potential	38 cm FSD
(d) Mo-anode	30 kV tube potential	

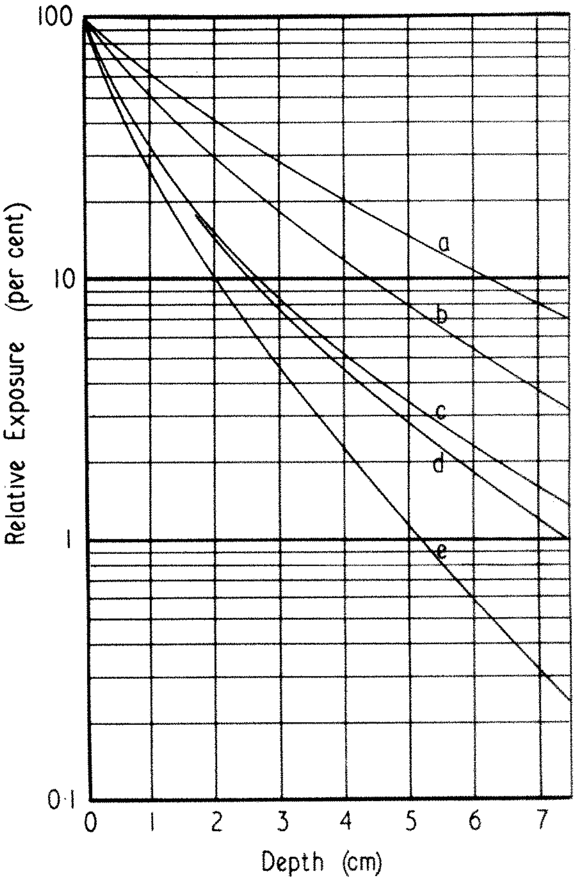


FIG. 4.

Variation of exposure through muscle-equivalent material for the two X-ray régimes represented in Fig. 2.

(a) W-anode	50 kV tube potential	82 cm FSD
(b) W-anode	30 kV tube potential	
(c) Mo-anode	50 kV tube potential	38 cm FSD
(d) Mo-anode	45 kV tube potential	
(e) Mo-anode	30 kV tube potential	

years' experience within the Royal Marsden Hospital using a Mammomat molybdenum anode X-ray tube and the Xerox 125 system (Gillbe, 1973). There was no explicit attempt to compare film with Xerox plates in a controlled trial, but both media were in use during the period, and the exposure factors for each were therefore well established. It can be seen that in every case the higher kV X-ray beam results in a lower skin exposure. Even when the criterion chosen is the energy absorbed from the beam (interpolated from Table I) the final column in Table II confirms that this is appreciably lower for the 45–50 kV beam used in xeromammography. The table also demonstrates the great importance of adequate compression of the breast as a means of reducing the energy absorbed.

RADIOLOGICAL PROCEDURES OTHER THAN MAMMOGRAPHY

It has been shown that xeroradiography has some advantages in venography and arteriography (James *et al.*, 1973), in the radiology of bones and joints (Wolfe, 1969), and in various aspects of head and neck radiology. In all these sites the Xerox technique must compete with film used with intensifying screens and a comparison of the patient exposure incurred can only be made by measuring the skin exposure when the two systems are used at the same FSD, but with the X-ray tube settings (kVp and mAs) chosen to give the optimum picture quality on the particular recording medium in use. In our work on this problem we have therefore cooperated with radiologists in several centres, and in each case we

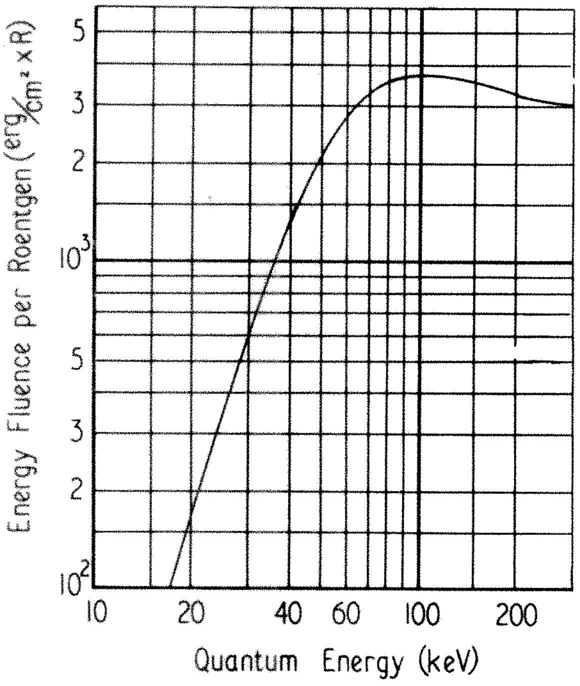


Fig. 5.
Energy fluence per röntgen as a function of quantum energy for monochromatic radiation.

measured the incident skin exposure for the normal X-ray setting used by the radiologist when taking a picture on film. We then reset the kVp and mAs to the values most appropriate for xeroradiography and took a confirmatory xeroradiograph, thereafter measuring the incident skin exposure to the patient at these settings.

It is not our purpose here to compare picture quality or information content; that demands a careful examination of the film itself versus the xeroradiograph, by an experienced radiologist and so we do not present any such comparison—merely a few xeroradiographs to demonstrate that these were satisfactory under the conditions chosen. Figure 6 shows that a xeroradiograph is not significantly degraded when the antiscatter grid is omitted, and for many procedures in which the film technique would require a grid the xeroradiograph is excellent without it. To minimize patient exposure, we frequently used the maximum kVp which the available X-ray equipment would give—often a nominal 120 kV, but the true potential frequently proved to be less than this when tested by a recently calibrated Ardran-Crooks cassette. If a higher tube potential had been available it would probably have been

TABLE I

Calculation of energy absorbed in an average breast for both Mo-anode and W-anode X-ray at tube potentials of 30 to 50kV.

Tube potential	Anode	Filter	Mean photon energy	Exposure calculation		Energy fluence per R	Fraction absorbed in 4 cm of tissue (50/50: fat/muscle)	Energy retained in 4 cm breast per cm² of beam area per R at surface
				Mean exposure photon	$\left(\frac{\mu_{en}}{\rho}\right)$ air			
kV			keV	keV	cm²/g	ergs/cm². R	(See Fig. 3)	ergs/cm². R
30	Mo	Mo 0·03 mm	17·2	15·8	1·10	85·8	0·97	83·2
40	Mo		18·9	16·8	0·90	109	0·95	104
50	Mo		20·9	17·5	0·80	130	0·93	121
30	W	Al 0·5 mm	19·8	17·0	0·88	115	0·82	94·3
40	W		23·6	19·0	0·61	177	0·77	136
50	W		27·2	20·8	0·45	253	0·72	182

TABLE II

STANDARD MAMMOGRAPHIC EXPOSURE SETTINGS FOR THE SIEMENS "MAMMOMAT" USED EITHER WITH NON-SCREEN FILM (KODAK PE 4006) OR XEROX PLATES ("125" SYSTEM) AT 45 CM FFD. THE "MAMMOMAT" HAS A ROTATING MOLYBDENUM ANODE WITH INHERENT FILTRATION 0·03 MM MOLYBDENUM.

Type of breast	Tissue thickness (under compression)	Technique used	Tube settings	Skin exposure (R)	Energy retained in breast ergs/cm^2
Small	~2 cm	Xerox 125	45 kVp 25 mAs	2·3	220
		Film	30 kVp 160 mAs	5·4	380
Medium	~ 4 cm	Xerox 125	45 kVp 50 mAs	5	560
		Film	30 kVp 320 mAs	12	1,000
Large	~ 6·5 cm	Xerox 125	50 kVp 125 mAs	15	1,950
		Film	30 kVp 640 mAs	24·6	2,110

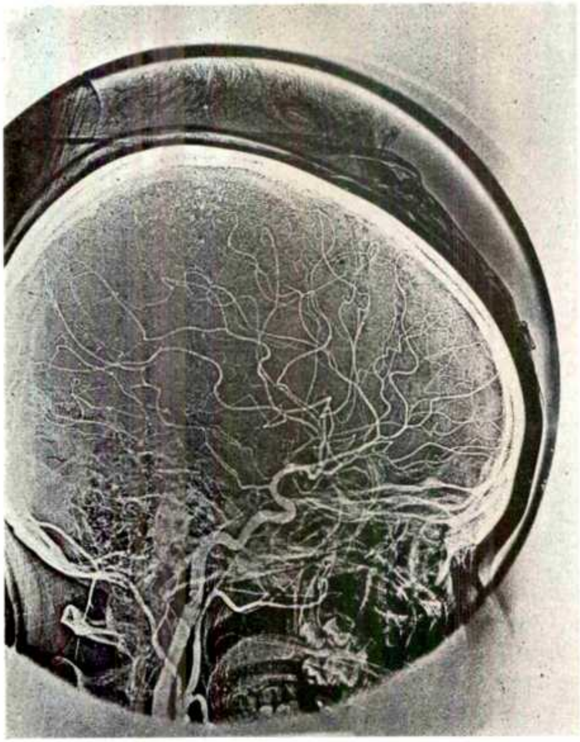


FIG. 6.
Carotid angiogram taken without antiscatter grid.

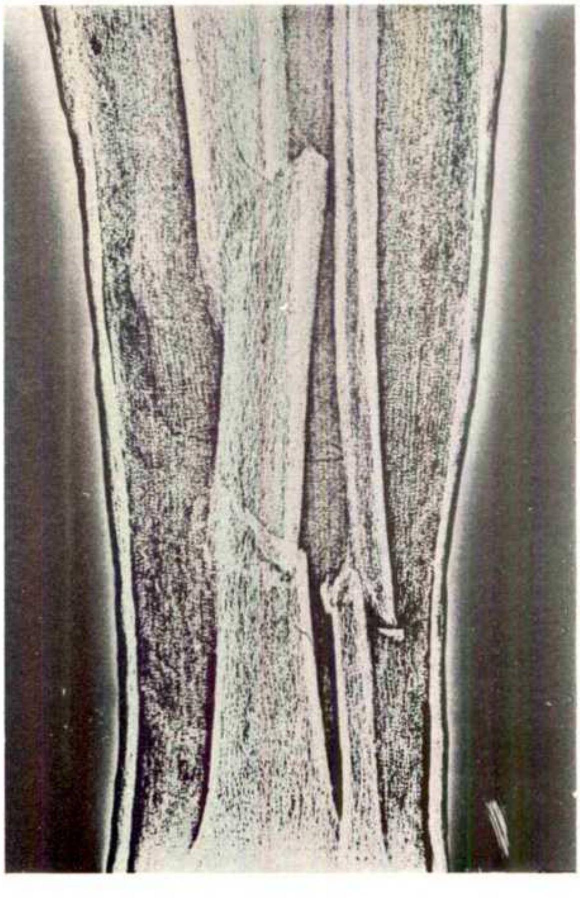


FIG. 7.
Xeroradiograph of fracture taken without removing plaster cast. Nominal tube settings 120 kV 24 mAs. (Subsequently found to be giving considerably lower voltage.)

TABLE III**

Skin exposure measurements for xeroradiography and film radiography in various radiological examinations.

Radiography			X-ray film			Xerox plates		
Case no.	Site	View	Tube settings	FSD (cm)	Skin exposure (mR)	Skin exposure (mR)	Tube settings	FSD (cm)
1	Left scaphoid	A–P	60 kV 10 mAs	84	64	96	100 kVp 5 mAs	84
		Lateral oblique	60 kV 16 mAs	83	134	106	105 kVp 5 mAs	83
2	Wrist	A–P	60 kV 10 mAs	84	64	96	100 kVp 5 mAs	84
		Lateral	60 kV 16 mAs	82	134	132	100 kVp 8 mAs	82
3	Scaphoid	A–P	60 kV 10 mAs	84	64	96	100 kVp 5 mAs	84
		Lateral	65 kV 16 mAs	82	119	146	115 kVp 6 mAs	82
		Lateral oblique	65 kV 10 mAs	84	75	106	105 kVp 5 mAs	84
4	Right elbow	A–P	62 kV 16 mAs	84	114	187	120 kVp 8 mAs	84
		Lateral	67 kV 16 mAs	82	130	187	120 kVp 8 mAs	82
5	Carotid angiogram	Lateral				1,150	125 kVp 40 mAs (with grid)	80
	(Figs. 5 and 6)	Lateral	72 kV 40 mAs (with grid)	80	394	385	125 kVp 16 mAs (no grid)	80
6	Skull (air contrast injections)	A–P	80 kV 80 mAs (with grid)	77	950	1,200	122kVp*50mAs (no grid)	77
		Lateral	71 kV 80 mAs (with grid)	82	620	690	122kVp*32mAs (no grid)	82
7	Carotid angiogram	A–P	78 kV 100 mAs (with grid)	77	1,160	1,200	122kVp*50mAs (no grid)	77
		Lateral	69 kV 80 mAs (with grid)	82	560	690	122kVp*32mAs (no grid)	82
8	Cervical spine	Lateral	75 kV 80 mAs (with grid)	150	190	330	108kVp*64mAs (no grid)	150

(The exposure measurements were made in "air" and do not include backscatter which amounts to some 20 per cent in most cases.)

* Measured values of kVp (effective), using Ardran-Crooks cassette.

**In all the work reported in this table the old Haloid manual equipment was used to develop the exposed plate and the powder image on the selenium surface was photographed directly on 6 × 6 cm film. It seems that the powder transfer process used in the fully automatix Xerox 125 system requires a greater powder density and therefore a radiation exposure which may be up to twice as high.

possible to obtain quite satisfactory xeroradiographs at somewhat lower patient exposure. The use of these higher tube potentials allows good pictures of fractures to be obtained without removing the plaster cast (Fig. 7).

The data in Table III indicate that certain radiological examinations on limbs, head, etc., can be made by xeroradiography using conventional X-ray equipment at high kV settings without much increase in the radiation exposure to the skin above that incurred by conventional screen-film techniques even although the intrinsic sensitivities of the two recording media differ by a large factor. This is due, as already mentioned, to the lower attenuation of the harder radiation which can be used and to the elimination of the need for grids. The dose to bone marrow and other deeper tissues will, however, be somewhat larger for the higher voltage radiation. The selenium thickness on the standard Xerox plates is 130 μm, and the sensitivity of such a layer will be only slightly lower at 187 kV than at 129 kV (Shneideris *et al.*, 1968; see Boag, 1973, Fig. 6). An exploration of xeroradiography at higher kVp and, in the long run, for thicker selenium layers would therefore seem to be well worth while.*

A further factor in patient exposure is the number of films needed for a particular examination. The wider latitude of the xeroradiograph often shows diagnostic detail in regions of widely different density on the one picture, where two or more separate films at different exposures would be required.

For all the sites shown in Table III, the scatter dose to the gonads should be negligible, so the hazard to be considered is principally the bone marrow dose. Although for equal exposure at the incident skin surface the higher energy beam will give a somewhat higher exposure at deep-seated bone marrow, the factor for converting to absorbed dose will be smaller. Each radiological procedure would require a separate discussion to arrive at an accurate numerical assessment of marrow dose, but it seems clear from Table III that the differences between conventional film techniques and xeroradiography need not be large, and may well permit the use of the latter technique for examinations where the gonad dose is negligible.

Acknowledgments

We are much indebted to Dr. M. Marshall and Dr. L. H. J. Peaple of A.E.R.E., Harwell, for providing the calculated spectral data on the two X-ray beams we used. We thank our radiological colleagues who allowed us to make these measurements in their departments: Drs. J. J. Stevenson and J. S. Macdonald of the Royal Marsden Hospital; Professor J. R. Martin and Mr. K. L. G. Mills of the University of Dundee; Dr. J. Ambrose and Dr. G. Hart of the Atkinson Morley Hospital.

REFERENCES

Ardran, G. M., and Crooks, H. E., 1968. Checking diagnostic X-ray beam quality. *British Journal of Radiology*, *41*, 193–198.

Boag, J. W., 1973. Xeroradiography—review article. *Physics in Medicine and Biology*, *18*, 3–37.

Gillbe, P., 1973. Xeroradiography of the breast. *Radiography*, *39*, 127–135.

Gray, L. H., 1940. Physical investigation of the contribution of the photo-electrons from sulphur to X-ray ionization. *British Journal of Radiology*, *13*, 25–30.

James, P., Baddeley, H., Boag, J. W., Johns, H. E., and Stacey, A. J., 1973. Xeroradiography—its use in peripheral contrast angiography. *Clinical Radiology*, *24*, 67–71.

Marshall, M., and Peaple, L. H. J., 1974. Private communication.

Marshall, M., Peaple, L. H. J., Ardran, G. M., and Crooks, H. E., 1975. A comparison of X-ray spectra and outputs from molybdenum and tungsten targets. *British Journal of Radiology*, *48*, 31–39.

Palmer, R. C., Egan, R. L., Tanner, B. K., and Barnette, P. A., 1971. Absorbed dose in mammography using three tungsten and three molybdenum target tubes. *Radiology*, *101*, 697–699.

Shneideris, M., Ambrozaitis, K., and Kavalyauskas, R., 1968. In *Medical Xeroradiography*. (Vilna, U.S.S.R.: Mintis) (in Russian with English summary).

Wolfe, J. N., 1969. Xeroradiography of the bones, joints, and soft tissues. *Radiology*,, *93*, 583–587.

Young, G. B., 1974. Techniques and radiation in mammography. *British Journal of Radiology*, *47*, 811–815.

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*We now use 150 kV for some of the sites listed in Table III.

Book review

Quantitative Nuclear Cardiography. Edited by Richard N. Pierson, Jun., Joseph P. Kriss, Robert H. Jones and William J. MacIntyre, pp. 289 (illus.), 1975 (John Wiley & Sons), £12·00.

This multi-author book follows closely on the heels of a somewhat similar volume on cardiovascular nuclear medicine which was recently reviewed in this journal (*48*, 673 (1975)), and many of the contributors are the same. The essential differences are that the arrangement of the information in the present volume is rather more problem-orientated as distinct from a survey of techniques, and the coverage is restricted to the heart, with the emphasis on quantitative haemodynamic measurements.

The major chapters cover the use of dynamic imaging techniques for studies on the normal heart and in patients with congenital or acquired heart disease. Analysis of left ventricular function and regional myocardial perfusion studies are also covered. The technical chapters cover the mathematical modelling of radiocardiographic data, instrumentation and radiopharmaceuticals. The brief concluding chapter on imaging of myocardial infarcts is an extremely up-to-date (September, 1974) account of the important recent developments in this field.

Although the main emphasis is on the quantitative analysis of radiocardiographic data, there are numerous illustrations showing sequential images in a wide variety of clinical disorders, so that the book can serve as a comprehensive atlas of radioisotope angiographic appearances. In all, it represents another useful survey of a rather specialized but potentially important subject, and can be recommended as an extremely competent review.

N. Veall.

1975, *British Journal of Radiology*, 49, 262–266

Stability of a linear accelerator with "achromatic" electron beam bending

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(*Received May, 1975, and in revised form October, 1975*)

Abstract

Third-generation accelerators with 270 deg. "achromatic" electron-beam bending should combine compact construction with improved stability. Two-year performance records are presented to show that flatness has remained within ±1 per cent with the first production model of the Radiation Dynamics "Dynaray-4" accelerator installed in Cardiff.

Medical linear accelerator development falls into three well-defined phases:

(1) first-generation machines with "in-line" construction, 1950–60;
(2) second-generation machines with 90 deg. electron bending, 1960–70;
(3) third-generation machines with 270 deg. electron bending, 1970–.

First-generation machines were large, with limited rotation, but were stable in use. The 90 deg. electron bending of the more compact second-generation machines is energy-sensitive, requiring servo stabilization techniques to maintain an adequate level of beam stability. Electron beam bending through 270 deg. can be made insensitive to large variations in electron energy, and therefore the new third generation accelerators with so-called "achromatic" or pretzel bending magnets should combine stable performance with compact construction. With accelerators of this general type available from at least three manufacturers, it is important to find out whether the stable performance expected from the achromatic magnet is achieved in clinical practice. This paper gives an account of the X-ray beam symmetry and stability of the first production model of the Radiation Dynamics 4 MeV "Dynaray-4" accelerator over a period of more than two years of hospital use.

Principle of Operation

Non-dispersive, or "achromatic" bending of an electron beam is produced by a non-uniform field between shaped poles shown schematically in Fig. 1. The electron beam enters the weak field where the pole gap is wide, through the so-called "mirror plane" defined by the two shaded surfaces of the magnet in Fig. 1. An electron with low energy follows the smaller full-line loop trajectory, entering and leaving the field as if optically reflected from the "magnetic mirror" of the "mirror plane". An electron with higher energy follows a flatter trajectory at first (larger dotted loop) which takes it further into the narrow pole gap where the stronger field corrects the trajectory by the right amount so that both electrons leave the field through the same point in the mirror plane. A pretzel magnet, therefore, accepts electrons of any energy within the design limits and delivers them all to the same point on the centre of the target, *T*. In the uniform field of a 90 deg. bending magnet the electron of higher energy will follow a path of larger bending radius to hit the target off-centre. Because a conical filter is used to flatten the X-ray beam in all medical accelerators, any appreciable movement of the focal spot from the centre of the target results in an asymmetry of the X-ray beam which is clinically unacceptable. The number and variety of papers describing split-chamber beam steering, automatic frequency control, energy servo loops, etc., is adequate testimony to the problems of maintaining beam stability with the second generation accelerators of the past decade.

The magnetic mirror was first described by Kel'man *et al.* (1939) and developed independently for ion beam bending by Enge (1963). The position of the pretzel magnet in relation to the other main components is shown in the simple schematic, Fig. 2, of the Dynaray-4 accelerator. Achromatism is usually best for a bending angle slightly less than 270 deg., and the resulting outward tilt of the accelerating waveguide reduces the size of the supporting structure and leads to a more compact machine. The performance of a pretzel magnet is unaffected even by large changes in magnet current. The smaller loop in Fig. 1 shows the path followed by an electron at the lower end of the energy spectrum. If the magnet current is reduced, the same low energy electron moves out to follow the larger loop, but still hits the centre of the target. Electrons at the higher end of the energy spectrum would now be following a loop even larger than those sketched in Fig. 1, dangerously close to the wall of the vacuum box, so that in practice the first warning of a reduced magnet current is a rapid collapse of the vacuum due to outgassing from bombarded and overheated metal, but without any change in beam symmetry. For example, when the magnet current was deliberately held at 8 per cent below normal, the exposure rates at opposite sides of a 30 cm wide field were 102·2 and 102·0 per cent of the exposure rate at the centre, while the pressure in the vacuum system rapidly approached the safety trip point. Under these conditions, the mean exposure rate was reduced by 30 per cent, and the preferential removal of the electrons from the higher end of the energy spectrum showed up in the over-flattening of the X-ray beam by the small amounts mentioned.

BEAM SYMMETRY AND STABILITY

In order to achieve and maintain the high degree of beam flatness and stability which is possible with a pretzel machine, it is important that the position of the focal spot and the angle of incidence of the electron beam with the target should be in correct adjustment. Because the position of the focal spot on the target is independent of the magnet current over a wide range, centering of the spot on the target is done mainly by movement of the whole magnet assembly in one or more of the 6 deg. of freedom available (sliding or rotation relative to the x, y or z axis). During this adjustment, the central fixing screw of the flattening filter is replaced by

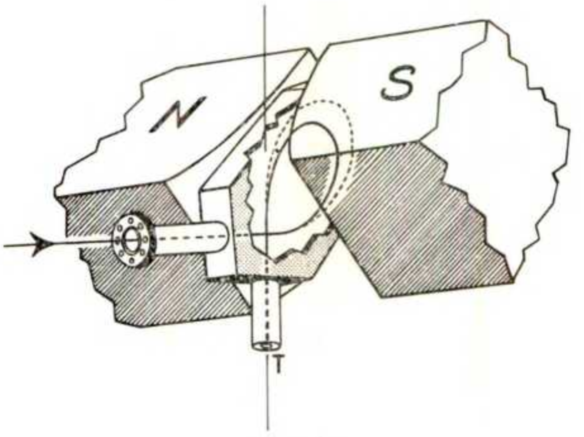

FIG. 1.
Sketch of the vacuum box and looped electron path in the non-uniform field of the shaped poles of a pretzel magnet.

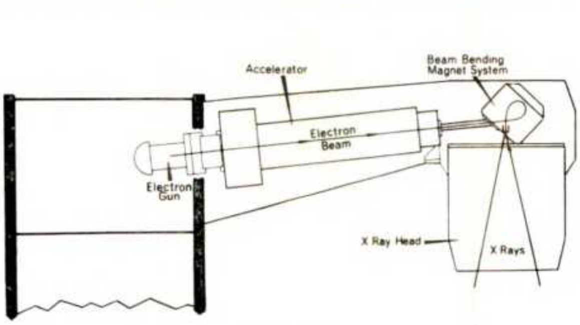

FIG. 2.
Relationship of pretzel magnet to other main components of the Dynaray-4 accelerator.

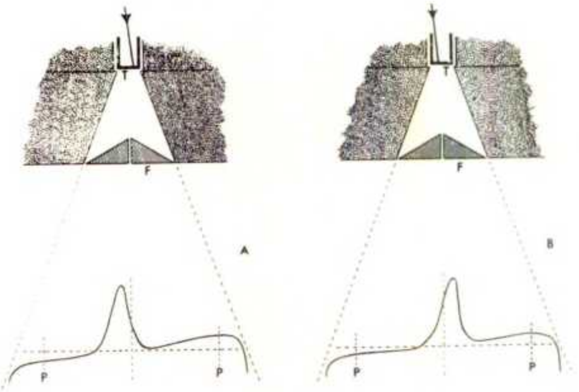

FIG. 3.
Experimental arrangement used to monitor position of spot and angle of incidence of electrons on accelerator target.

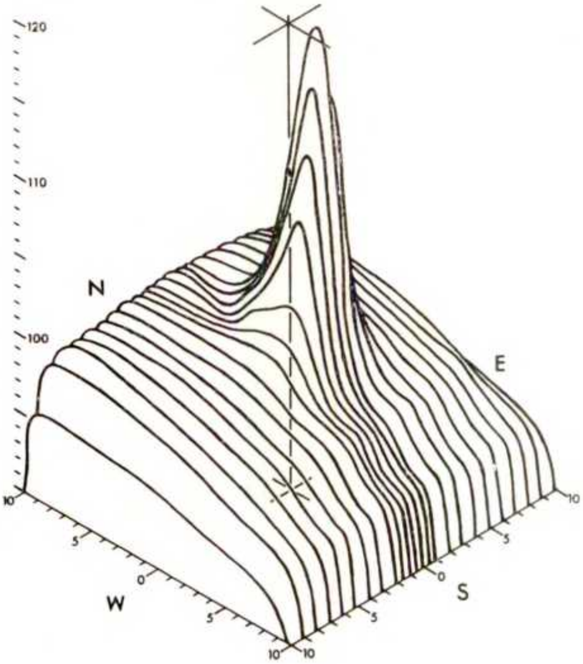

FIG. 4.
Pinhole beam superimposed on flatness profiles from an incorrectly adjusted bending magnet. The vertical dotted line represents the central axis of the X-ray beam.

a screw with a small hole drilled along its axis, to form a "pinhole" imaging system, as shown schematically in Fig. 3. The distance of the focal spot from the centre of the target can be estimated from the displacement of the pinhole image from the central axis, if the magnification of the system is known. If the electron beam is not hitting the target perpendicularly, the resulting tilt in the polar emission of X rays will show up as an asymmetry between any pair of widely spaced points outside the pinhole beam and equidistant from the axis (P, P in Fig. 3).

Figure 4 shows an isometric plot of results of the type described, obtained during early on-site commissioning of the Cardiff machine. Exposure rate contours were measured in air with a microchamber (Sutherland, 1964) at a focus-chamber distance of 185 cm, chosen to give a tenfold magnification of pinhole image displacement, and with a diaphragm setting which gave a "field" of about 20×20 cm at the measuring distance. In the direction convention adopted for the Dynaray-4, and used in the figures accompanying this paper, the supporting structure of the accelerator (annulus) is south from the isocentre. The focal spot was found to be displaced from the centre of the target by 0·8 mm towards North and 1·0 mm towards West (displacements are reversed in a pinhole projection). The general asymmetry of the beam showed that the electrons were also not hitting the target perpendicularly, as shown schematically in Fig. 3A. This small amount of maladjustment could be corrected by a compromise setting of the various beam steering and focusing currents to achieve a clinically satisfactory degree of flatness, but with a small loss of exposure rate. Instead, with all other parameters optimized for maximum exposure rate, the pretzel magnet was readjusted to put the spot on the centre of the target, with the result shown in Fig. 5. With the magnet readjusted in this way, the final beam symmetry is shown in Fig. 6, measured in air at 100 cm over the full 30×30 cm maximum available field. Except for the two central and the four corner "warm spots" flatness is within ±1 per cent over the whole field.

As a first step in the commissioning of the machine, while it was still under test at the factory, the

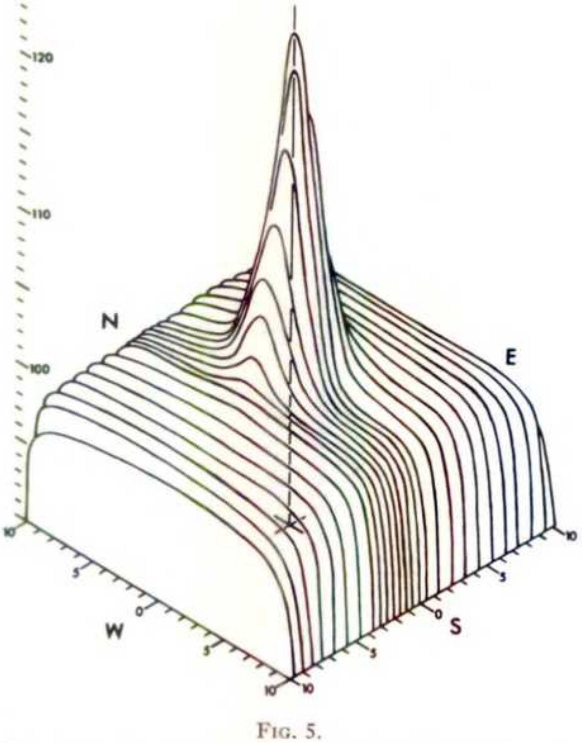

FIG. 5.

Pinhole beam superimposed on flatness profiles from a correctly adjusted bending magnet. The vertical dotted line represents the central axis of the X-ray beam.

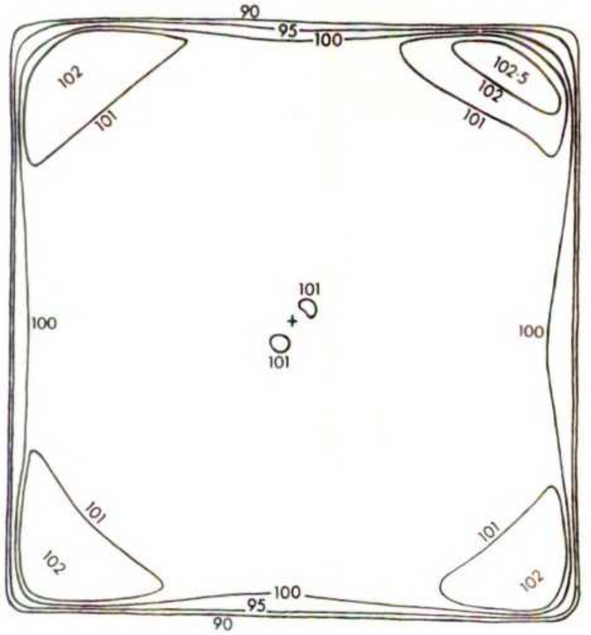

FIG. 6.

Flatness contours of full 30×30 cm field, measured in air at 100 cm.

electron beam energy was raised to about 4·6 MeV to achieve an exact match of water depth-dose values with an existing accelerator, so that treatments would be fully interchangeable between the two machines. The electron gun fitted in the Dynaray-4 is space-charge-limited, so that electron injection is almost independent of cathode temperature over the working range, and is controlled only by the diameter of a small hole in the gun anode. Since this hole cannot change in use, the gun design produces very constant electron loading of the RF wave, which in turn produces a stable electron beam energy. This feature contributes to the high overall stability of the X-ray beam, and even makes it difficult to produce deliberate changes in X-ray beam energy. Therefore the required increase in X-ray energy to match the existing accelerator had to be obtained by substituting a new anode plate with a smaller diameter hole, thereby decreasing the electron loading of the RF wave. As a result, the higher energy X-ray beam was underflattened by the existing filter, and metal was machined progressively from the periphery of the conical filter to obtain the degree of flattening described in this report. The reduction in the diameter of the filter at the base of the cone caused the four small regions of slightly higher exposure rate in the extreme corners of the 30 × 30 cm field. Since this novel feature is clinically beneficial, to help maintain dose-rate out to the edges of large treatment volumes, it was not considered necessary to replace the filter with one designed for the higher energy. The two central warm spots of +1 per cent are caused by a combination of effects due to the small central mirror of the beam defining light system used in the Dynaray-4, and the absence of metal from the screwdriver slot of the central screw which secures the conical flattening filter.

The extent to which the flatness of Fig. 6 will be maintained under all conditions of use, and over the years, constitutes the most severe test possible for the practical value of achromatic electron bending in actual clinical use. Early results from the Cardiff machine are summarized in the final two figures, which together add up to a remarkable record of beam stability. Figure 7 shows the stability of beam flatness during a 360 deg. rotation of the machine. Flatness was measured along the axis of rotation of the accelerator, at 100 cm in air across a 30 cm field, with the microchamber supported by a floor-mounted, remotely driven exploring unit. The changing direction of the beam relative to the floor-mounted chamber caused the latter to pass through the two central "warm spots" of Fig. 6 differently at each angle, resulting in the variations in the appearance of the two small "bumps" on the traverses of Fig. 7. The ±2 per cent limits are shown dotted for each traverse. Apart from the central variations mentioned, flatness deviations do not exceed ±1 per cent over the full 360 deg. rotation. Finally, Fig. 8 shows a sequence of traverses with the beam pointing vertically down, starting with the machine in the factory and then extending over more than two years of hospital use. The traverses are plotted on an expanded scale (relative to Fig. 7) in order to show that even the fine structure has been maintained. The following comments refer to Fig. 8:

(1) Curve A was measured in the factory without a beam-defining light system in the treatment head, and therefore shows some small differences from the other traverses.

(2) Between curves B and C the small mirror of the

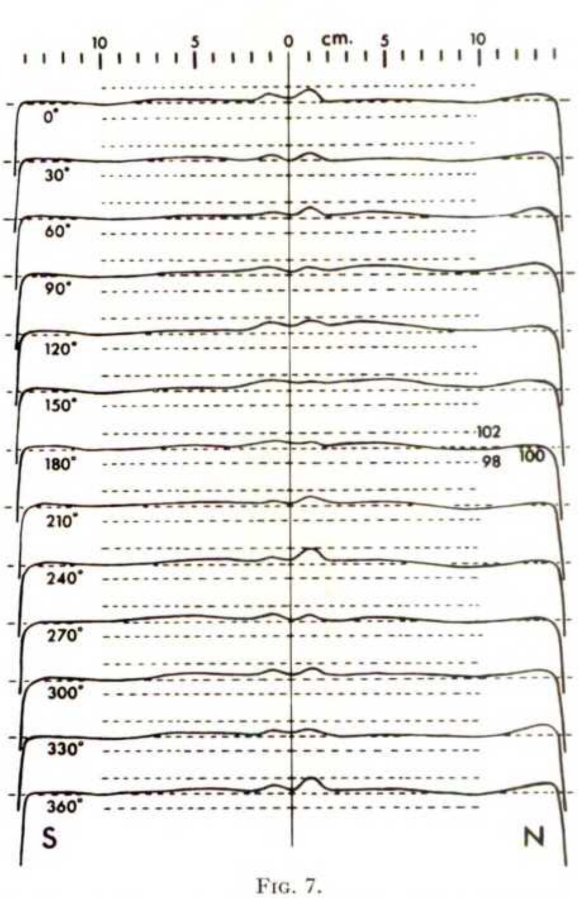

FIG. 7.

Flatness profiles measured across 30 cm field at 100 cm during full rotation of accelerator.

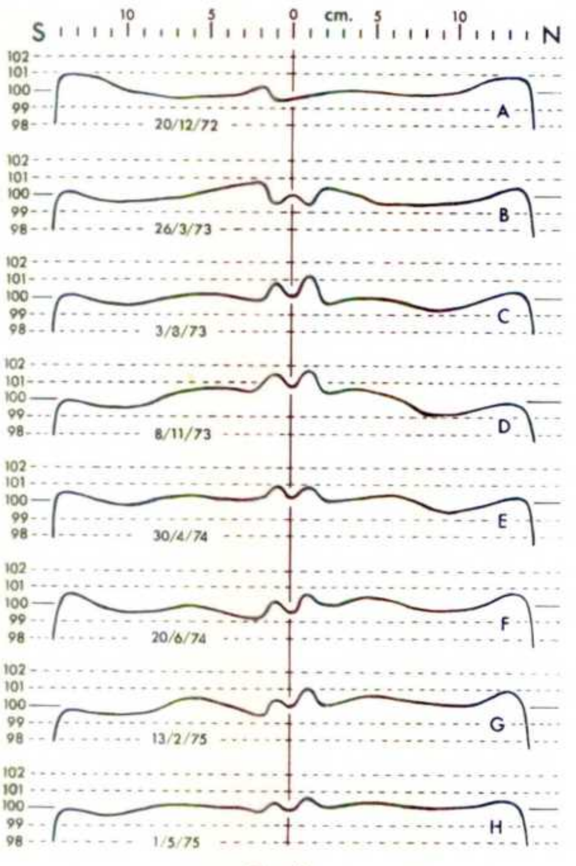

Fig. 8.

Flatness profiles during two years of use, measured across 30 cm field at 100 cm.

beam-defining light system was modified, producing a change in the central fine structure, which thereafter remains stable within experimental limits.

(3) Between curves C and D the pretzel magnet was removed for addition of extra lead shielding.

(4) Curve D was measured at a time when the electron emission was dropping rapidly from a failing cathode. It shows the slight increase in beam energy resulting from partial failure of the space-charge-limiting effect in the electron gun, and represents the worst conditions likely to arise in practice from gun malfunction. Even under these conditions no asymmetry is visible.

(5) Between curves D and E the pretzel magnet was removed for fitting a new target of slightly different design.

(6) Between curves G and H the poles of the pretzel magnet were removed to cure a vacuum leak by tightening the fixing bolts around the base of the vacuum box. No readjustment of any kind was necessary before measuring curve H.

(7) During the period covered by Fig. 8 five cathode changes took place, showing that flatness (and therefore also X-ray beam energy) is not likely to be affected by small differences from one cathode to another.

Except for the variation in the way in which the microchamber passes through the two central warm spots each time the measuring equipment is set up, these records show that flatness has been maintained to better than ± 1 per cent over two years of use, without any special efforts or readjustments after the initial setting up exercise. This has been in spite of the above selection from the possible catastrophies that can happen to an electron bending system in clinical use.

REFERENCES

Enge, H. A., 1963. Achromatic magnetic mirror for ion beams. *Review of Scientific Instruments*, *34*, 385–389.

Kel'man, V. M., Korsunskii, and Lange, F. F., 1939. The magnetic electron mirror. *Journal of Experimental and Theoretical Physics*, *9*, 681–684.

Sutherland, W. H., 1964. Microchambers for dose rate exploration in high energy beams. *Acta Radiologica*, *2*, 209–218.

1976, *British Journal of Radiology*, *49*, 267–269 MARCH 1976

Technetium-99m labelled imidodiphosphate: an improved bone-scanning radiopharmaceutical

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(*Received July, 1975*)

ABSTRACT

Technetium-99m labelled imidodiphosphate was prepared in the presence of stannous ions. It was evaluated as a bone-scanning agent in animals and patients. Comparative tissue distribution studies in mice showed a relatively higher uptake of radioactivity in bone when ^{99}Tc^{m}-imidodiphosphate was used, as compared to ^{99}Tc^{m}-labelled pyrophosphate and diphosphonate. Accumulation of radioactivity in soft tissues, especially kidneys, was less with this radiopharmaceutical. Results in patients were most satisfactory in delineating skeletal bone and identifying bone lesions with relatively small tracer doses of the radiopharmaceutical.

Comparative studies with ^{18}F, ^{87}Sr^{m} and ^{99}Tc^{m}-labelled phosphate complexes have indicated the advantages of ^{99}Tc^{m}-labelled disphosphonate and pyrophosphate for bone scanning (Hosain *et al.*, 1973; Dunson *et al.*, 1973; Ackerhalt *et al.*, 1974). Pyrophosphate and diphosphonate with P-O-P and P-C-P linkages, respectively, have many similarities with the P-N-P grouping of imidodiphosphate (Larsen, Willett and Yount, 1969; Robertson and Fleisch, 1970; Fleisch *et al.*, 1973). Recently, Subramanian *et al.* (1975) have reported ^{99}Tc^{m}-labelled stannous imidodiphosphate to be a promising bone-scanning agent due to its higher uptake in the animal skeleton. Independently, we have been investigating a related preparation and obtained excellent results not only in animals, but also in clinical evaluations.

MATERIALS AND METHODS

Preparation

Preliminary studies were carried out with sodium imidodiphosphate and stannous chloride to determine optimal labelling with ^{99}Tc^{m} for skeletal imaging. It was observed that a simple method of preparation, essentially similar to that for pyrophosphate (Hosain, 1973), gave reproducible results. A 1·2 per cent solution of stannous chloride ($SnCl_2.2H_2O$) in $\frac{1}{3}$ N HCl was added to a 1·2 per cent solution of sodium imidodiphosphate ($Na_4NHP_2O_6.10H_2O$) in isotonic saline in a 1:10 ratio by volume; the pH was close to 6·6. The latter material was supplied by Boehringer Mannheim Corp. and stated to be 99 per cent pure. Kits were prepared by transferring 0·5 ml. aliquots of the mixture through a 0·22μ membrane filter into sterile rubber-capped vials, which were flushed with nitrogen gas. These kits were stored in a freezer. Each kit contained an equivalent of 2·2 mg of imidodiphosphoric acid and 0·26 mg of tin(II). At the time of use, an appropriate amount of ^{99}Tc^{m}-pertechnetate eluate (1–80 mCi in 0·5–3 ml.) was added to the vial at room temperature to obtain ^{99}Tc^{m}-imidodiphosphate complex.

Evaluation

Paper chromatographic studies were carried out, using 85 per cent methanol and 15 per cent water, to determine the presence of free pertechnetate in the radiopharmaceutical.

Experimental scanning was carried out in rabbits weighing approximately 2 kg. A tracer dose of 0·5–0·8 mCi containing 0·1–0·3 mg of the complex was injected intravenously for bone scanning. A rectilinear scanner (Picker Magnascanner-V) was used to obtain posterior views covering the thoraco-abdominal region at different times.

Blood clearance and urinary excretion measurements were carried out in four female dogs weighing between 13 and 15 kg. They were anaesthetized with sodium pentobarbital and catheterized for the collection of urine. A slow infusion of isotonic saline (about 100 ml./hour) was maintained during the experimental period of four to five hours. Blood samples and urine were collected at hourly intervals following intravenous injection of 0·2–0·5 mCi of the radiopharmaceutical.

Tissue distribution studies were carried out in mice (approximately nine weeks old). They were sacrificed at different times, particularly at two hours, following intravenous injection of tracer doses of ^{99}Tc^{m}-imidodiphosphate diluted in isotonic saline (5–10 μCi containing about 20 μg of the complex in

0·2 ml. dose). Similar studies were carried out with $^{99}\mathrm{Tc}^{m}$-labelled pyrophosphate and ethylidenediphosphonate. $^{99}\mathrm{Tc}^{m}$-pyrophosphate was prepared according to the method of Hosain (1973) and $^{99}\mathrm{Tc}^{m}$-diphosphonate was prepared according to the method of Dunson *et al.* (1973). They were flushed with nitrogen gas.

Application

The radiopharmaceutical was used in human investigations. Kits were used after testing for sterility and apyrogenicity of the batches. One kit was used for as many as five patients, each receiving 10–12 mCi of the agent intravenously within two hours after addition of pertechnetate. Scans were obtained between one and five hours, after administration of the tracer dose, by using a dual probe rectilinear scanner (Ohio Nuclear). Thus far 18 patients, who were referred for bone scanning for the evaluation of possible bone metastases or to define the extent of metastases, have been studied.

RESULTS

Chromatographic studies of the radiopharmaceutical preparations, used in the human investigations, indicated the presence of less than 0·5 per cent of free pertechnetate. Clear delineation of the skeletal bone in rabbits, with negligible radioactive accumulation in liver and kidneys, was noted upon scanning about one hour after administration of dose. In dogs, approximately 2 per cent of the radioactivity was found in the total blood at two hours and about 40 per cent was excreted in the urine during that period. Tissue distribution studies in mice showed relatively higher accumulation of radioactivity in the bones from $^{99}\mathrm{Tc}^{m}$-imidodiphosphate as compared to other $^{99}\mathrm{Tc}^{m}$-labelled phosphate complexes (Table I).

TABLE I

COMPARATIVE TISSUE DISTRIBUTION IN MICE SHOWING RADIOACTIVITY IN RELEVANT ORGANS AT TWO HOURS FOLLOWING INTRAVENOUS INJECTION OF TRACER DOSES OF $^{99}\mathrm{Tc}^{m}$-LABELLED DIFFERENT PHOSPHATE COMPLEXES

	% dose/organ (mean ± S.D. for six mice)		
Organs	Imidodiphosphate	Pyrophosphate	Diphosphonate
Blood (calculated)	0·52 ± 0·15	0·93 ± 0·14	0·35 ± 0·09
Liver	0·49 ± 0·11	0·57 ± 0·12	0·38 ± 0·12
Kidneys	0·44 ± 0·10	0·76 ± 0·14	0·52 ± 0·11
G.I. with content	1·37 ± 0·20	1·26 ± 0·19	1·18 ± 0·16
Two femurs	2·47 ± 0·17	1·94 ± 0·18	1·71 ± 0·16

Results in all 18 patients were most satisfactory. Skeletal bones, especially metastatic lesions, were clearly delineated. Figure 1 illustrates an example of the skeletal scan without any metastatic lesions. Figure 2 shows the scan with extensive bone metastases.

DISCUSSION

The behaviour of $^{99}\mathrm{Tc}^{m}$-imidodiphosphate appeared to be similar to that of $^{99}\mathrm{Tc}^{m}$-labelled pyrophosphate and diphosphonate. However, uptake in the bones (as evident in the femurs of mice)

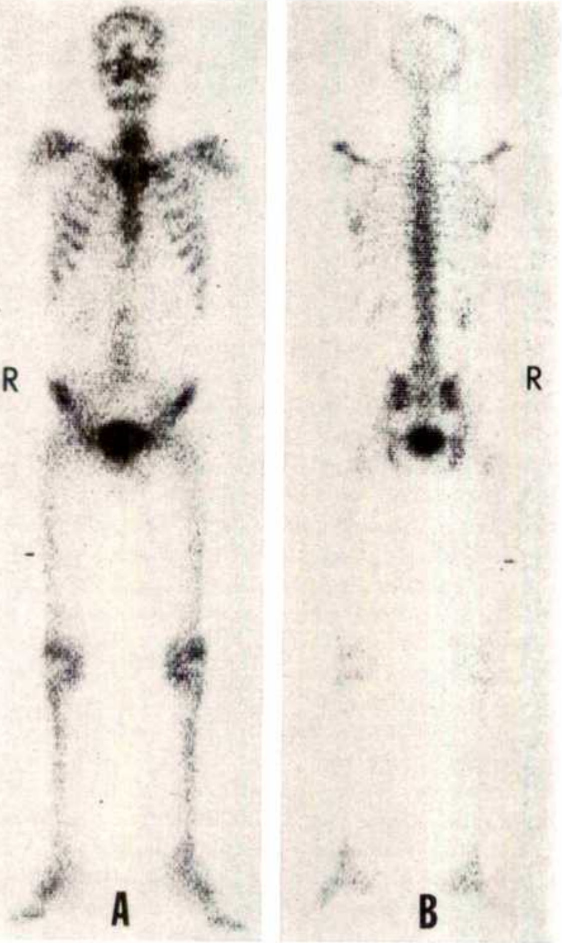

FIG. 1.

Skeletal scans showing anterior (A) and posterior (B) views of a patient without any lesion in bone. A 51-year-old man with suprapubic pain for six months was referred for bone scanning. The patient did not have any renal disease but had colitis.

was about 25 and 50 per cent greater than that occurring with ^{99}Tc^{m}-labelled pyrophosphate and diphosphonate, respectively. Uptake in the kidneys was particularly low with ^{99}Tc^{m}-imidodiphosphate. The advantage with this agent was that the scans could be obtained with relatively smaller tracer doses of ^{99}Tc^{m}. Indeed, 10–12 mCi of this radiopharmaceutical was used for scanning adult human subjects instead of the usual 15–20 mCi doses of the other two complexes.

Stannous-imidodiphosphate kits could be prepared, evaluated and stored in a frozen condition for human use. The kits could also be lyophilized specifically for commercial purposes. Storage of kits in a frozen condition has been found convenient, and a similar agent (Sn-pyrophosphate complex) has been found stable for over a year in that condition (Hosain, 1975). Inferior preparations of all the ^{99}Tc^{m}-labelled phosphate complexes, intended for bone scanning, usually show higher uptake of radioactivity in the soft tissue, particularly the liver (Hosain, 1975). The present method of preparing the ^{99}Tc^{m}-imidodiphosphate has produced a product with consistently low soft-tissue uptake.

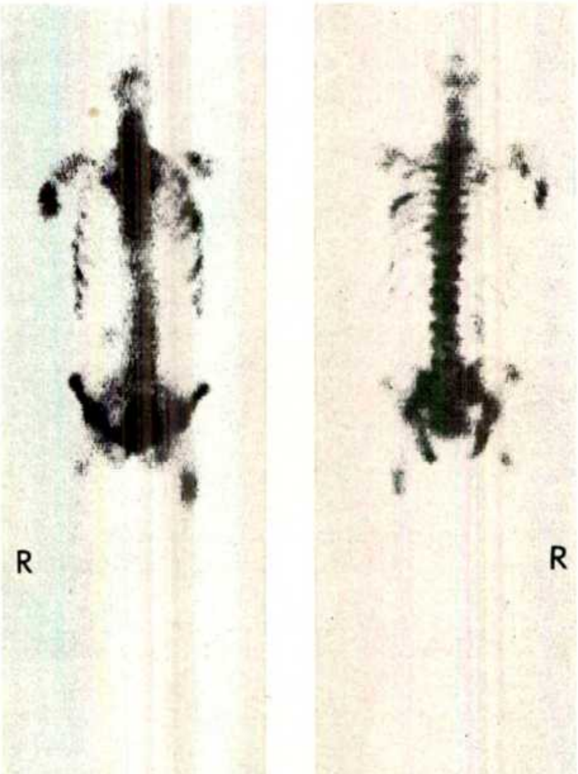

FIG. 2.

Skeletal scans showing anterior (A) and posterior (B) views of a patient with extensive metastatic lesions in bone. A 59-year-old man with adenocarcinoma of prostate with metastases was referred for bone scanning prior to chemotherapy.

Most of the human scans were obtained at about three hours after the administration of the tracer dose, but it was observed that adequate scans could be obtained as early as one hour. Radioactive uptake in liver and kidneys was low. It was also noted that the uptake in normal bone in patients with extensive metastases was relatively low compared to the normal bone of patients without any metastasis. This becomes evident when Figs. 1 and 2 are compared. It appears that this radiopharmaceutical provides a higher target to non-target ratio, and the agent is probably superior to the presently used ^{99}Tc^{m}-labelled phosphate complexes.

ACKNOWLEDGMENTS

This work was partially supported by the American Cancer Society Grant DT-34E and the United States Public Health Service Grants CA-17802 and GM-10548.

REFERENCES

ACKERHALT, R. E., BLAU, M., BAKSHI, S., and SONDEL, J. A., 1974. A comparative study of three ^{99m}Tc-labelled phosphorus compounds and ^{18}F-fluoride for skeletal imaging. *Journal of Nuclear Medicine, 15*, 1153–1157.

DUNSON, G. L., STEVENSON, J. S., COLE, C. M., MELLOR, M. K., and HOSAIN, F., 1973. Preparation and comparison of technetium-99m diphosphonate, polyphosphate and pyrophosphate nuclear bone imaging radiopharmaceuticals. *Drug Intelligence and Clinical Pharmacy, 7*, 470–474.

FLEISCH, H., RUSSELL, R. G. G., BISAZ, S., and BONJOUR, J. P., 1973. The effect of pyrophosphate and diphosphonate on calcium metabolism. *Hard tissue growth, repair and remineralization*, Ciba Foundation Symposium 11, pp. 331–348 (Associated Scientific Publ., New York).

HOSAIN, F., HOSAIN, P., WAGNER, H. N. jun., DUNSON, G. L., and STEVENSON, J. S., 1973. Comparison of ^{18}F, ^{87m}Sr, and ^{99m}Tc-labeled polyphosphate, diphosphonate and pyrophosphate for bone scanning. *Journal of Nuclear Medicine, 14*, 410.

HOSAIN, P., 1973. Technetium-99m labelled pyrophosphate: a simple and reproducible bone scanning agent. *British Journal of Radiology, 46*, 724–728.

1975. Development of technetium-99m labelled pyrophosphate and use in the study of dynamics of fracture healing. Doctor of Science Thesis, Johns Hopkins University, Baltimore, pp. 24–31.

LARSEN, M., WILLETT, R., and YOUNT, R. G., 1969. Imidodiphosphate and pyrophosphate: possible biological significance of similar structures. *Science, 166*, 1510–1511.

ROBERTSON, W. G., and FLEISCH, H., 1970. The effect of imidodiphosphate (P-N-P) on the precipitation and dissolution of calcium phosphate *in vitro*. *Biochimica Biophysica Acta, 222*, 677–680.

SUBRAMANIAN, G., MCAFEE, J. G., ROSENSTREICH, M., COCO, M., 1975. Tc-99m labeled stannous imidodiphosphate (Tc-99m-IDP): evaluation of a new bone imaging agent. *Journal of Nuclear Medicine, 16*, 574.

1976, *British Journal of Radiology*, *49*, 270–277

The measurement of the performance of the display system of a radioisotope imaging device: the multi-element band display

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(*Received July, 1974 and in revised form June, 1975*)

Abstract

An assessment has been made of the performance of the type of display system in which each display signal intensity, *i.e.* grey shade or colour, represents a range of count densities or counting rates. In the particular commercially available system used in this investigation eight different grey shades are used to display the image, a range of count densities being allocated to each grey shade.

It is shown experimentally that changes in the distribution of radioisotope can fail to be detected solely due to the manner in which the display is used, viz. the way in which the count density is allocated to the available grey shades. Also, it is shown experimentally that the best display performance can be achieved by using one in which the range of count densities represented by each grey shade is less than three standard deviations of the mean background count density.

Although several investigations have been made into display performance (Mallard and Wilks, 1968; Vauramo, 1970; Schulz *et al.*, 1970), there still appeared to be a need to produce results using a very simple, yet clinically realistic, test-pattern under carefully controlled conditions.

The main purpose of clinical radioisotope investigations is to detect a small change in an otherwise normal distribution of radioisotope. Although some investigators, *e.g.* Schulz *et al.*, 1970, prefer to take as the normal pattern that of the distribution of radioisotope in a particular organ, it was felt that there was both difficulty in defining such a normal pattern, due to anatomical variations between patients, and also that most clinical patterns were too complicated to be suitable for a study of display systems. Instead a uniform distribution of radioisotope was chosen as the simplest possible normal pattern. This is not completely divorced from having any clinical meaning since, for example, the central area of a lateral brain scan shows such a uniform distribution of radioisotope. The abnormality consisted of a circular area of increased activity 2 cm in diameter. This size was felt to be representative of the smaller size of lesion routinely detected in clinical practice. A measure of display performance is then an assessment of how, as the intensity of the normal pattern changes, the intensity of the abnormality must vary so that it is detected. These intensities are, of course, expressed as count densities or counting rates.

The effect on the visual system of changing physical conditions, such as viewing distance, has been investigated by several workers (De Palma and Lowry, 1961; Davidson, 1968), although not specifically in relation to radioisotope images. Their results emphasized the need to control the physical parameters under which the display records are viewed; this has been done in this investigation. In addition, it is also necessary to control the psychological conditions. Whether or not an observer claims that he can see the abnormality depends upon the criterion used when making the decision. If the observer gave a positive response (indicating that he could see the target) only when absolutely certain of his judgement, then this observer would produce fewer true positive responses (*i.e.* correct detections of the target) than one who gave a positive response to any signal which might indicate a target. However, the latter observer would also give more false positive responses (*i.e.* positive responses to signals which are not the target). A signal detection theory proposed by Tanner and Swets (1954) postulated that true and false positive responses were linked such that an increase in the rate of true positives could only be achieved at the expense of increasing the number of false positives.

In this set of measurements it was intended that both the physical and psychological conditions under which the observers operated should not only be controlled as much as possible but should also resemble those met in clinical practice as closely as possible.

Most of the reported measurements of display performance have been carried out using systems providing signals of brightness proportional to the intensity of the radiation from the detected activity, *e.g.* the photo-scan and the gamma camera oscilloscope display. However, the system considered in this paper is one of a type becoming increasingly popular, in which the display uses only a limited number of different intensities (usually grey shades or colours) to portray the detected activity. Thus each grey shade or colour represents a range of values of count density or counting rate. Such displays will be referred to as band displays since a range or band, referred to as the band width, of count densities or counting rates is represented by each different signal on the display.

METHOD

The display system used for this investigation consisted of a multi-parameter analyser coupled to a P.D.P. 8/I computer (Nuclear Data 50:50 system). The display consists of a 64×64 matrix of square elements generated on a cathode ray tube. The number of counts (detected γ photons) associated with an element is indicated by the brightness of the element, this brightness being one of eight different grey shades. In this paper these shades will be denoted by the series SH1, SH2 . . . where SH1 is the darkest shade and SH8 the brightest. The display is addressed either directly by a gamma camera or indirectly from a punched paper tape produced by a rectilinear scanner (Bowley *et al.*, 1973).

As has already been mentioned, the test pattern consisted of a uniform distribution of radioactivity, referred to here as the background, on which was superimposed the abnormality, or target, consisting of a circular area of radioactivity. The size of the background was chosen so as to correspond to that of the field of view of the gamma camera used with this display, this being circular in area and 31 cm in diameter. The resulting image on the display had a total of 3,096 elements, each element representing a square area of the radioisotope distribution of side 5 mm. On this scale the target image was represented by a total of 12 elements.

In order to obtain a true measure of display performance which must be independent of the distortions imposed by a real imaging system, such as a gamma camera or scanner, the input signal to the display was simulated. Punched paper tapes representing a uniform distribution of radioactivity were produced on the rectilinear scanner with a phial of radioisotope attached to the collimator of the detector. This input to the display was then manipulated by the computer to produce the desired image of the background. The target was produced by extracting a small circular area from a displayed uniform background which had the required mean counts per element (CPE). It was superimposed upon the chosen background to simulate the test-pattern. This results in a rectangular count density profile across the target which has the advantage of removing any effects due to a particular collimator's response.

For each chosen value of the mean background CPE, a series of targets were superimposed, ranging in intensity from those which could be seen easily in the displayed image, to those which were undetectable. About five different mean target values were chosen to span this range. For each target value ten different display records were produced, equivalent to ten different scans. The target was in a different place each time. In addition, ten display records were produced showing the background alone. Since it was not feasible to use the cathode ray tube display directly to show the image to each observer, Polaroid photographs were taken as a record of each different image. It was, of course, necessary to choose a photographic exposure which allowed the observer to recognize all the different grey shades which were present in each particular image.

Each set of photographs was presented to a series of observers having varying clinical experience in judging such display records. The photographs were presented randomly in a viewing box which was designed to ensure that each person saw them under identical and standardized conditions. These conditions were chosen so as to represent those found in clinical practice; the viewing distance was 33 cm and the average brightness of the display record was about 8·5 cd/m^2 (2·5 ft. La).

Each observer was instructed carefully to report as positive only those records on which he was absolutely certain that the target was present, and to give its position. The remaining records which could have been classified as either equivocal or negative, were collectively regarded as negative.

With each set of 60 photographs every observer was first given a trial run to allow him to learn how to apply the decision criterion. Then five more presentations were made, spaced at least a day apart, to produce experimental results for each observer. The number of true positive answers out of the 50 answers that an observer gave for each target value (expressed as a percentage) was taken as the average visual response given by an observer, for a particular target intensity. These average response values were then plotted for a range of values of the target CPE, the background CPE being the same in each case. Typical results are shown in Fig. 2 where each line represents the response from one observer. The largest error in measuring visual response is that in determining the 50 per cent response point. To a good approximation each visual response curve will be S-shaped;* by fitting such a curve to the experimental points, the fractional standard, deviation of the target intensity corresponding to 50 per cent visual response was estimated to be less than 10 per cent. This is sufficiently accurate for this experiment, in which altogether a total of over 20,000 responses were determined.

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*Strictly the curve was assumed to be an ogive. Probit analysis, as described by Finney (1952) was used to fit the curve to the experimental data.

RESULTS

A typical example of a display record is shown in Fig. 1.

Figure 2 shows a typical set of visual response curves. Each curve shows how, for each observer, his response varied with target count density, the background count density being kept constant. Visual response is given as the fraction (expressed as a percentage) of true positive answers given by the observer.

For example, point A in Fig. 2 which is 6 per cent, means that when that observer viewed the ten pictures of this target of 6 CPE above background on five separate days, he gave a positive response on three out of the 50 occasions. The percentage of false positive responses given by observers when using the particular decision criterion chosen for this experiment is negligible and will be ignored in the results reported here.

As can be seen from Fig. 2, there is a variation between the responses given by different observers even though they have all been instructed to use the same decision criterion. A separate experiment showed no correlation between clinical experience in the use of this display and visual response, a result which has been reported in the review by Mallard (Fig. 16, 1974).

The average value over all observers of those target intensities above background needed to produce a 50 per cent visual response was taken as being representative of each set of curves (see Fig. 2). The ratio of this target count density (above background) to the mean background count density will be called the DETECTION CONTRAST. The detection contrast, then, is that ratio of target to background intensity needed to give the observer a 50 per cent chance of correctly detecting the target.

Two forms of band display were considered.

1. *Constant band-width*

In this type the range of count densities represented by each grey shade (*i.e.* the band-width) was kept constant for all values of the background count density. This range was 32 CPE, the darkest shade (shade SH1) being assigned to all elements having between 0 and 31 counts, while the brightest grey shade (shade SH8) represented elements having from 224 to 255 counts.

After experimental measurements of detection contrast were made at backgrounds of 22, 27, 32, 57, 64, 80, and 128 CPE, a method was devised whereby measurements made for one value of the background count density could be extrapolated to give the detection contrast at other background

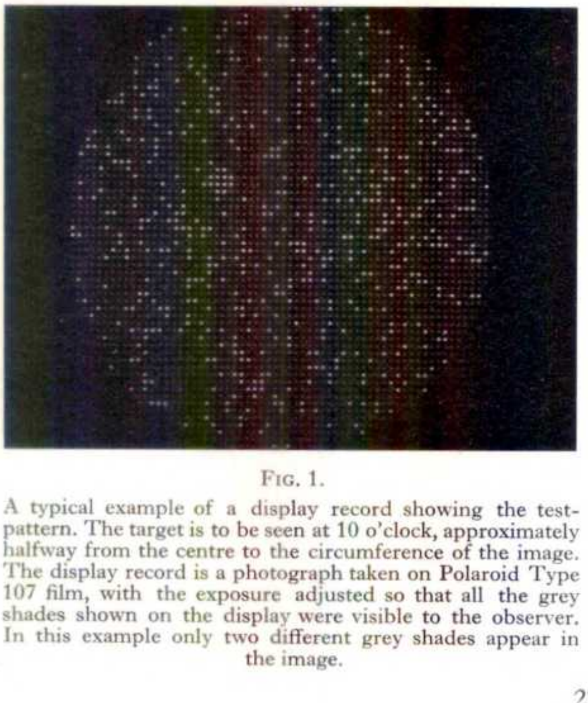

FIG. 1.

A typical example of a display record showing the test-pattern. The target is to be seen at 10 o'clock, approximately halfway from the centre to the circumference of the image. The display record is a photograph taken on Polaroid Type 107 film, with the exposure adjusted so that all the grey shades shown on the display were visible to the observer. In this example only two different grey shades appear in the image.

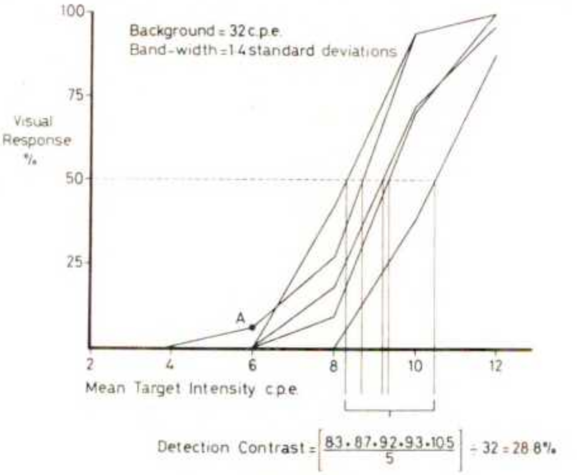

FIG. 2.

Visual responses given by the set of observers. Each curve shows the variation of the fraction of true positive answers (expressed as a percentage) given by one observer, with target intensity. (N.B. Target intensity is that CPE in the target which is added to the background CPE.) Also marked are those values which produced a 50 per cent visual response from each of the observers, namely targets with average count densities of 8·3, 8·7, 9·2 and 10·5 CPE. The calculation of the detection contrast from these values is shown.

values. This was done because it was not feasible to make the very large number of experimental measurements which would have been needed to measure how the detection contrast varied over a wide range of background density. This method of extrapolation is described in Appendix I.

Figure 3 shows how experimental and extrapolated values of detection contrast vary with background count density when the band-width is 32 CPE.

2. *Statistical band-width*

The second form of display was the statistical band-width (Mallard *et al.*, 1964; Laughlin *et al.*, 1969; Keyes and Gillespie, 1970). With this the range of count densities represented by one grey shade is always equal to a constant number of standard deviations of the mean background count density.

In the clinical case, the mean background count density surrounding any abnormality is not known in advance. As a result, the range of count densities represented by each grey shade or colour is made equal to a chosen number of standard deviations of that count density at the centre of the band (see Keyes and Gillespie, 1970). This means that the range of count densities represented by one shade will increase from SH1 to SH8. This arrangement is obviously an approximation to a true statistical band system but probably represents the best which can be done in clinical circumstances.

In this experiment, however, the mean background count density is always known. As a result, each grey shade can now be made to represent the same number of standard deviations of the background count density. For example, if the background count density is 64 CPE, then to represent a statistical band-width of, say, three standard deviations each grey shade must cover a range of 24 CPE.

With the statistical band-width form of the display used in this experiment, it was possible to vary the number of standard deviations represented by each grey shade (the band-width) and also the position of each grey shade relative to the chosen background count density. When the position is altered, the values of count density for the boundaries between each shade will also change. This effect is shown in

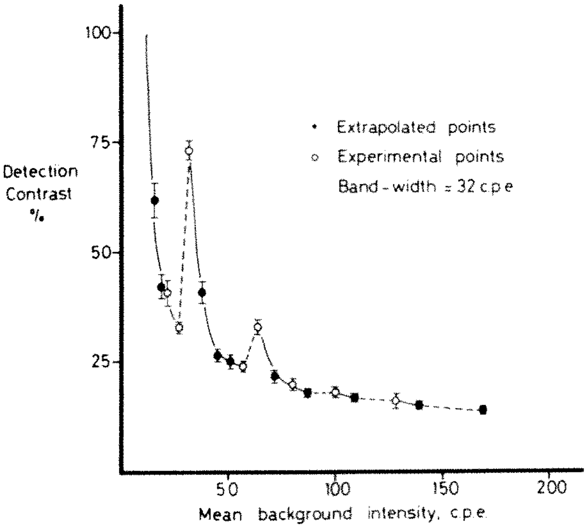

FIG. 3.

Effect on the detection contrast of changing the mean background CPE. Detection contrast is that contrast needed for the observer to have a 50 per cent chance, on average, of seeing the target. The display is the constant band-width one. The dotted lines show the probable behaviour of the curve where the extrapolation procedure of Appendix I cannot be used. The error bars show the variation in detection contrast between different observers.

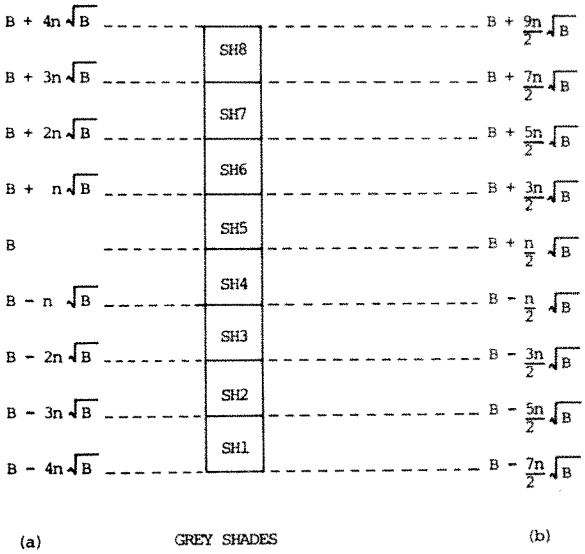
$B + 4n\sqrt{B}$
$B + 3n\sqrt{B}$
$B + 2n\sqrt{B}$
$B + n\sqrt{B}$
B
$B - n\sqrt{B}$
$B - 2n\sqrt{B}$
$B - 3n\sqrt{B}$
$B - 4n\sqrt{B}$
SH8
SH7
SH6
SH5
SH4
SH3
SH2
SH1
$B + \frac{9n}{2}\sqrt{B}$
$B + \frac{7n}{2}\sqrt{B}$
$B + \frac{5n}{2}\sqrt{B}$
$B + \frac{3n}{2}\sqrt{B}$
$B + \frac{n}{2}\sqrt{B}$
$B - \frac{n}{2}\sqrt{B}$
$B - \frac{3n}{2}\sqrt{B}$
$B - \frac{5n}{2}\sqrt{B}$
$B - \frac{7n}{2}\sqrt{B}$
(a)
GREY SHADES
(b)

FIG. 4.

Effect of the positioning of the statistical bands relative to the background count density, B, on the range of count densities represented by each grey shade. The statistical band-width is n standard deviation.

(a) Background count density coincident with the maximum count density represented by grey shade SH4.

(b) Background count density equal to the average count density represented by grey shade SH4.

LIBRARY

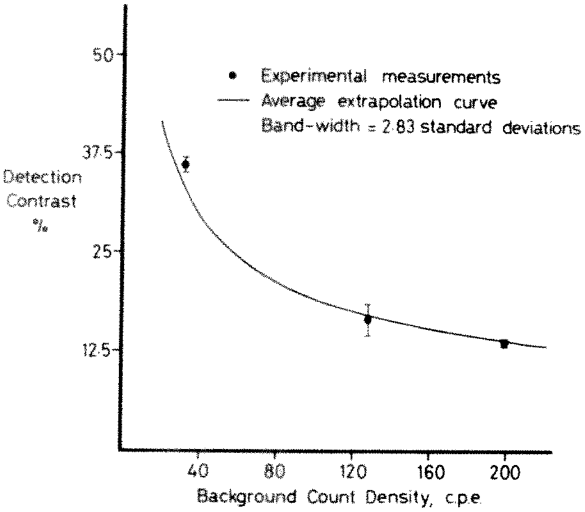

Fig. 5.

The effect of count density on detection contrast when the statistical band-width is kept constant. Two experimental measurements are shown. The curve is produced by the extrapolation procedure of Appendix II. In this case the curve is the average of the three curves produced from the three experimental points.

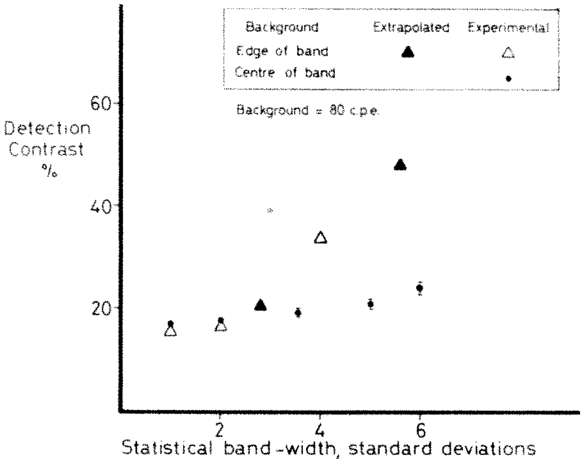

Fig. 6.

Effect of statistical band-width on detection contrast. For one set of points the background count density corresponds to the centre of a band, in the other set it is the same as the band limit.

Fig. 4 for two extreme cases. In Fig. 4a the background count density is coincident with the maximum count density represented by one of the grey shades, *i.e.* the background count density is at a band-limit. In Fig. 4b, the background density is equal to the average count density shown by one particular grey shade, *i.e.*, it is at the centre of a band.

As with the constant band-width system a method was evolved to use the experimental measurement of detection contrast at one value of the background count density to predict the detection contrast at other background values, assuming that the statistical bandth-width and the position of the background in the band remained unchanged; this method is described in Appendix II. Figure 5 shows the results of measurements of detection contrast at background count densities of 32, 128 and 200 CPE. The band-width was 2·8 standard deviations throughout, and the background count density was coincident with a band limit. As can be seen, there is good agreement between the points and the average extrapolated curve.

Detection contrast was also measured for a series of different statistical band-widths, but with the background count density and its position within the band fixed. The experimental and extrapolation results are shown in Fig. 6. For the lower curve the background count density corresponds to the centre of a band whatever its width, *i.e.* it has a value equal to the average of the maximum and minimum count densities of the band in which it is situated; the upper curve shows the variation in detection contrast when the value of the background count density corresponds to that of a band limit.

Discussion

The preceding results show that in band display systems the detectability of a small change in image intensity is influenced by three parameters. Firstly, as can be seen from Fig. 6, increasing the statistical width of the band, while keeping all other parameters constant, can cause the detection contrast to increase, *i.e.* a greater target intensity is needed for detection. This effect is observed for band-widths of greater than three standard deviations when the background is at the edge of a band and for band-widths of greater than about five standard deviations when the background is at the centre of the band.

The second factor is the position of the mean background count density relative to the band limits. This is important for band-widths greater than three standard deviations. For example, it can be seen from Fig. 6 that at a band-width of five standard deviations the detection contrast is 21 per cent when the background is at the centre of a band but it rises to 40 per cent when the background is at the edge of the band. However, for statistical band-widths of less than three standard deviations there is no difference between the detection contrast values when the background is at the centre of a band and when it is at the edge. This is confirmed by Fig. 7, which shows a series of values of detection contrast measured when the background count density is at four different positions inside a band. As can be seen, there is no significant change in detection contrast. For the band-widths of less than three standard deviations, a target's detectability is not affected by the positioning of the bands relative to the mean background count density.

This result is important in clinical work where the mean background density, *i.e.* that around the abnormality, is not known precisely. If a statistical display system is used with a band-width of not greater than three standard deviations of the mean background count density, then the target will be equally well detected no matter where the background count density comes within the display scale.

This result is supported by a mathematical analysis by Keyes (1973) which suggested that a value of between one and a half and three standard deviations should be the optimum band-width. However, studies by Jordan and Geisler (1973), using a liver phantom, suggested that the optimum band-width should be slightly higher, between three and four standard deviations. However, this value was not rigorously measured. Further investigations on this point are in progress.

The third and final influence on detection contrast is the value of the mean background density. The effect on detection contrast of changing only the mean background count density was shown in Fig. 5. There is an approximately reciprocal square root relationship where a doubling of the background count density causes the detection contrast to decrease by a factor of 1·4, *i.e.* as the background count density increases, target detection becomes easier.

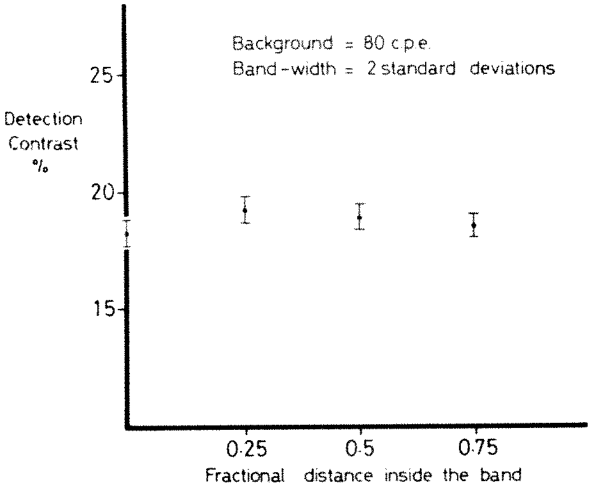

FIG. 7.

Variation of detection contrast with the position of the background inside the band of a statistical band-width display. At a fractional distance 0 the background count density corresponds to a band limit, at 0·5 it is at the centre of the band and at 0·25 and 0·75 it is one quarter and three quarters up from the lower band limit.

These results can be used to explain the results in Fig. 3 which showed the effect on the detection contrast of increasing the background count density when the display system was a constant band-width one of 32 CPE. This curve has a saw-tooth shape. Initially the detection contrast decreased with increasing background count density, as expected, until a background count density was reached at which it suddenly increased rapidly before starting to fall once again. This saw-tooth behaviour was repeated several times although the later increases were not as great as the first one. As can be seen from Fig. 3, a small increase of the background count density from 27 to 32 CPE causes the detection contrast to rise from 28 to 73 per cent. As a result, a target which would have been easily detected at a background of 27 CPE cannot be seen when the background is 32 CPE. This effect has not we believe, previously been demonstrated experimentally.

With the constant band-width system, as the background count density increases the number of standard deviations represented by the constant band-width will decrease; also the position of the background inside the band will change. For example, at a background of 16 CPE and a band-width of 32 CPE the statistical width of the bands is eight standard deviations and this particular background count density corresponds to the centre of a band. At a background of 64 CPE, the band-width has decreased to four standard deviations and the background count density is now at the edge of a band.

From the results found on the statistical band-width system, an increase in background count density and a decrease in statistical band-width both cause a decrease in detection contrast. This behaviour also occurs with the constant band-width system, as shown in Fig. 3 where the average trend of the detection contrast is that it decreases with increasing background count density. The sudden rises in detection contrast seen in Fig. 3 must be due to the effect of the change of the position of the background inside the band.

A comparison between Fig. 3 and Fig. 7 shows clearly the advantages of using a statistical scale for

TABLE I

AVERAGE DISTRIBUTION OF GREY SHADES AMONGST THE BACKGROUND ELEMENTS OF THOSE DISPLAY RECORDS USED TO TEST THE HYPOTHESIS ABOUT THE MANNER OF TARGET DETECTION

Background CPE	Band-width CPE	Mean number of elements having grey shade							
		SH1	SH2	SH3	SH4	SH5	SH6	SH7	SH8
32	32	1,476	1,620	0	0	0	0	0	0

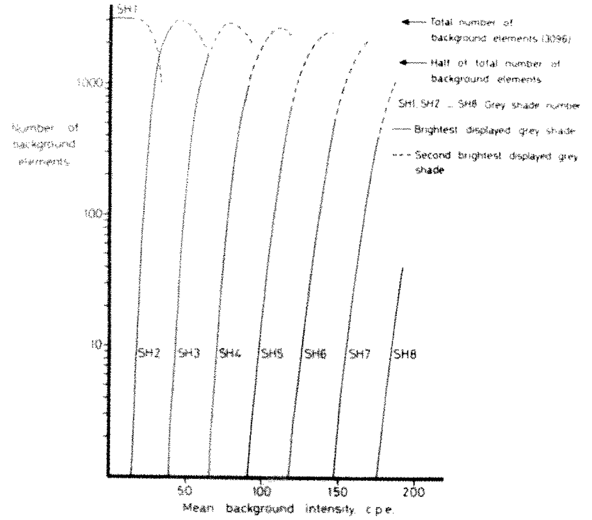

FIG. 8.

The variation in the number of background elements having the two brightest displayed grey shades, with mean background count density, for the constant band-width display. The band-width is 32 CPE.

displays and Figs. 6 and 7 show that band-widths of less than three standard deviations should be adopted. By following this procedure, one can ensure the most effective use of the available counts, and reduce the number of abnormalities missed through differences in the display.

ACKNOWLEDGMENTS

Part of this work was carried out while one of the authors (P.S.) was in receipt of a scholarship from the Medical Research Council.

Much help was given by Dr. T. J. Buchanan of the Department of Medical Physics and Mr. A. Bursill of the Department of Psychology, University of Aberdeen, and is very gratefully acknowledged.

APPENDIX I

The extrapolation procedure used with the constant band-width display.

The visual signal received from the display has two components. Firstly, the particular grey shade of an element gives an indication of the number of counts associated with it. Secondly, the distribution of elements of a particular grey shade shows the spatial extent of those areas having a similar count density.

TABLE II.

PERCENTAGE VISUAL RESPONSE FROM A SET OF OBSERVERS, AS A FUNCTION OF THE NUMBER OF ELEMENTS IN THE TARGET HAVING THE BRIGHTEST DISPLAYED SHADE OF GREY (SH3)

	Number of brightest elements				
Observer	0	1	2	3	4
A	0	0	0	100	100
B	0	0	100	100	100
C	0	0	100	100	100
D	0	0	100	100	100
E	0	3	94	100	100
F	0·5	43	100	100	100

It was noted in preliminary experiments that when about half of those elements making up the background image had the same shade of grey, the target was not seen unless some of the elements representing the target had the next brightest grey shade. This observation was confirmed by producing a set of display records, the details of which are given in Table I. As can be seen, the background consists of elements having only the first two of the eight available grey shades (*i.e.* shades SH1 and SH2). About half of the elements have each of these two shades. If the preliminary observation is true then the target should be detected only when some of the target's elements are of the next brightest grey shade (*i.e.* shade SH3).

In Table II the visual response given by each observer is shown as a function of the number of elements in the target having grey shade SH3. When none of the target elements have this grey shade then the observers failed to detect the target. The only positive responses were from observer F and those were negligible.

Now, if it should be that target detection is based only on the number of elements in the target which have the brightest shade in this particular image, shade SH3, and is not affected by the presence in the target of elements of shade SH2, then the visual responses shown in Table II should either be 0 or 100 per cent. That is, the observer either always sees the target every time that it has a particular number of elements having shade SH3, or, he always rejects it. This is observed to be the case with all but observers E and F. A statistical investigation of these two particular sets of results showed firstly no correlation between the two observers' results and secondly that the responses of observer F were probably random.

The results from this experiment, therefore, indicate that when more than half of the elements in the background have a particular grey shade then those elements in the target which have this same shade play no part in the detection of the target. The only elements in the whole image which influence detection are those which have a brighter grey shade, a target being detected when it has the appropriate number of elements of this brighter grey shade.

Figure 8 shows how the number of background elements having the two brightest grey shades to be shown in the image varies as the mean background count density increases. For example, when the background has a count density of between 20 CPE and approximately 40 CPE, shade SH2 is the brightest one present in the image and SH1 is the second brightest grey shade. At just over 40 CPE the third grey shade appears in a few elements and so SH2 replaces SH1 as the second brightest grey shade in the image.

Also marked in Fig. 8 is a line indicating half the total number of background elements. When the number of second brightest elements exceeds this value then, according to the results above, these elements have no effect on target detection. It is as if the background image only consisted of those elements which have the brightest grey shade displayed. Therefore, so far as target detection is concerned, images of the background for several different count densities now become identical. For example, images of the background at count densities of 27, 57 and 87 CPE, all contain 590 elements having whichever happens to be the brightest grey shade to be displayed in each image. The remainder of the 3,096 elements in the background have darker grey shades, of course. Also, in all four cases more than half of the background elements have whichever is the second brightest grey shade in the image. So in each of these display records there are, on average, 590 elements which influence target detectability, *i.e.* which act as noise. Each of these four background count densities produces an image which is identical, from the point of view of trying to detect a target in it.

The detection contrast (that ratio of target to background count density needed to produce a 50 per cent visual response) was experimentally determined for a background of 27 CPE and was found to correspond to a target having 9 CPE in excess of the background. A target of this mean count density will produce, on average, nine elements having the brightest displayed grey shade, *i.e.* shade SH2 in this case. So, our extrapolation procedure allows us to say that when the background count density is increased to 57 CPE then the corresponding detection contrast will be that which produces in the target image, on average, nine elements of the brightest displayed grey shade. As can be seen by reference to Fig. 8 this shade will be SH3.

In a similar manner the detection contrast could be calculated for a background of 87 CPE.

An experimental measurement was made of the detection contrast when the background was 57 CPE. It gave a value of 24 per cent which compares favourably with the value of 23 per cent predicted by the extrapolation procedure. This appears to confirm the validity of using the extrapolation procedure.

APPENDIX II

The extrapolation procedure used with the statistical band-width display

One of the features of the statistical band-width display, as used in the idealized procedure of this experiment (see Fig. 4), is that when background count density alone is altered, *i.e.* without changing either the statistical width of the band or the position of the background within the band, then the appearance of the image of that background remains unchanged. By appearance is meant the proportion of the elements having each of the grey shades.

From an experimental measurement that appearance of the target which produces a 50 per cent visual response from the observer can be determined, and the ratio of the corresponding target count density to the background count density is, of course, the detection contrast.

Since background appearance remains unchanged when its count density is varied, then, provided the target count density is altered so as to keep the target appearance unchanged, the observer will always give the same 50 per cent visual response. The extrapolation procedure, therefore, simply consists of calculating, for each value of background count density, that target count density which is needed to maintain its appearance. The ratio of this new target count density to the new background count density will then give the new value of the detection contrast.

REFERENCES

Bowley, A. R., Taylor, C. G., Causer, D. A., Barber, D. C., Keyes, W. I., Undrill, P. E., Corfield, J. R., and Mallard, J. R., 1973. A radioisotope scanner for rectilinear, ARc, transverse section and longitudinal section scanning (ASS – The Aberdeen Section Scanner). *British Journal of Radiology, 46,* 262–271.

Davidson, M., 1968. Perturbation approach to spatial brightness interaction in human vision. *Journal of the Optical Society of America, 58,* 1300–1308.

De Palma, J. J., and Lowry, E. M., 1961. Sine-wave response of the visual system. II Sine-wave and square-wave contrast sensitivity. *Journal of the Optical Society of America, 52,* 328–335.

Finney, D. J., 1952. *Probit Analysis* (Cambridge University Press).

Jordan, K., and Geisler, S., 1973. Data display in scintigraphy by means of a high speed electrostatic digital plotter and special computer averaging techniques. *Medical Radioisotope Scintigraphy, I,* pp. 635–652 (I.A.E.A., Vienna).

Keyes, W. I., 1973. An analysis of multi-level scan display systems. *Physics in Medicine and Biology, 18,* 282–283.

Keyes, W. I., and Gillespie, P. J., 1970. A statistically designed colour ribbon for scanners. *Physics in Medicine and Biology, 15,* 573–575.

Laughlin, J. R., Kenny, P. J., Corey, K. R., Greenberg, E., and Weber, D. A., 1964. Localization and total body high energy gamma-ray scanning studies in cancer patients. In *Medical Radioisotope Scintigraphy, I,* pp.253–272 (I.A.E.A., Vienna.).

Mallard, J. R., 1974. Radiosotope imaging – The end of the beginning. *Arquivo de Patalogia,* xlvi, 1–26.

Mallard, J. R., Duggan, M. H., Myers, M. J., and Wilks, R. J., 1964. An analysis of quantitative colour display for scanning. In *Medical Radioisotope Scintigraphy, I,* pp. 423–449 (I.A.E.A., Vienna).

Mallard, J. R., and Wilks, R. J., 1968. Characteristics of display systems in scanning and a simple phantom procedure to evaluate the overall scanner performance. *Journal of Nuclear Medicine, 9,* 96–109.

Schulz, A. G., Knowles, L. G., Kohlenstein, L. C., Mucci, R. F., and Yates, W. A., 1970. Quantitative assessment of scanning-system parameters. *Journal of Nuclear Medicine, 11,* 61–68.

Tanner, W. P., and Swets, J. A., 1954, A decision making theory of visual detection. *Psychological Review, 61,* 401–409.

Vauramo, E., 1970. An investigation into visualisation problems in radioisotope scanning. *Acta Academiae Aboensis, Ser. B, 30,* 1–47.

1976, *British Journal of Radiology*, *49*, 278–280

Technical note

The angulation of radiotherapy machines in the treatment of inclined lesions

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(*Received February, 1975 and in revised form December, 1975*)

The treatment of inclined lesions on isocentric radiotherapy machines by suitable combinations of the machine's angular movements has been described by Besford *et al.* (1964) and by Fleming and Orchard (1974). The purpose of this paper is to generalize the equations of these authors, and present an alternative method for planning the treatment of inclined lesions.

DEFINITION OF ANGLES

A typical isocentric machine is illustrated in Fig. 1. The axes of rotation of the unit, the couch top and the diaphragms all intersect at the isocentre. Both the couch and diaphragm axes are perpendicular to the unit axis. The treatment angles of the unit may be defined as follows (all angles considered positive in a clockwise direction):

A = angle of arm of treatment unit to vertical (when viewed facing the unit);

C = angle of couch top to a line parallel to the unit axis of rotation (when viewed from above);

D = angle of diaphragm rotation from position where one side is parallel to the unit axis of rotation (when viewed along a ray from the source).

When the patient is positioned, prone or supine, on the treatment couch, an inclined lesion will in general be angled to both the horizontal and to the patient's longitudinal axis (*i.e.* the couch top axis). As lesion inclination is usually derived from the examination of radiographs taken in the same patient position, let:

α = lesion angle to the horizontal, in lateral radiograph;

β = lesion angle to patient's longitudinal axis, in antero-posterior radiograph.

(See Fig. 2.) The true angle of lesion to the horizontal (γ) is therefore given by: $\tan\gamma = \tan\alpha\cos\beta$.

In multifield radiotherapy treatments, the fields are usually arranged such that their central rays are contained in a plane, called the "treatment plane", in which the dose distribution is calculated. For a particular field, let:

θ = angle of the field central ray to the projection of the vertical, in the treatment plane.

The derivation of equations for the calculation of treatment angles A, C, D from angles α, β, θ depends on the selection of treatment plane. Two methods are considered below.

METHOD 1

Treatment plane perpendicular to the lesion axis

This is the method described in detail by Fleming and Orchard, who considered the situation where $\beta = 0$. Their equations, when converted to the above notation and simplified, become:

$A = \arccos(\cos\alpha \,.\, \cos\theta)$;

$C = \arctan(\sin\alpha/\tan\theta)$;

$D = \arctan(\tan\alpha/\sin\theta)$.

When $\beta \neq 0$, the true lesion angle to the horizontal becomes γ. These equations still apply if the couch is rotated through $-\beta$ and angle α is replaced by γ, thus

$$\left.\begin{aligned} A &= \arccos(\cos\gamma.\cos\theta) \\ C &= \arctan(\sin\gamma/\tan\theta) - \beta \\ D &= \arctan(\tan\gamma/\sin\theta) \\ \text{Where } \gamma &= \arctan(\tan\alpha \,.\, \cos\beta) \end{aligned}\right\} \qquad (1)$$

For this method, each field direction is perpendicular to the lesion axis. As the treatment plane is not perpendicular to the patient axis, the fields enter the patient obliquely so that some form of missing tissue compensation is required to ensure a uniform dose along the lesion volume.

METHOD 2

Treatment plane vertical and perpendicular to patient axis

This selection of treatment plane makes $A = \theta$, and $C = 0$.

Diaphragm twist D may be calculated by considering the projection of lesion length in the treatment plane, as in Fig. 3.

Let L be the true lesion length. The projected lesion length (y) parallel to the patient axis, as measured in both radiographs, is given by:

$$y = L\cos\phi$$

and the projected lesion length in the treatment plane is ($L\sin\phi$).

A field angled at θ to the vertical will see this length foreshortened to (x) in the treatment plane, given by:

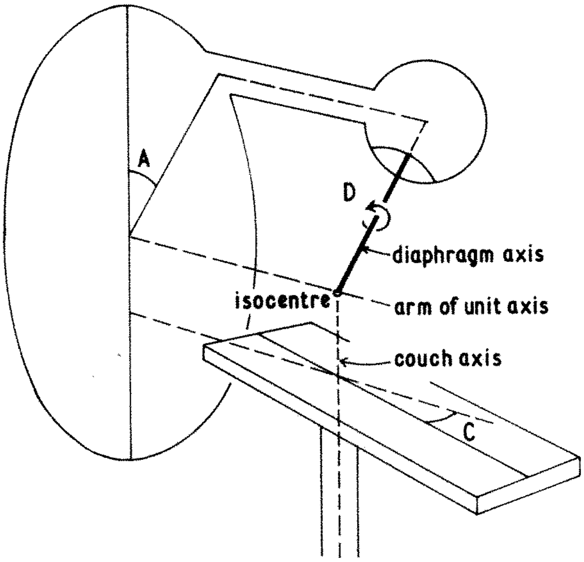

FIG. 1.
An isocentric treatment machine, showing the treatment angles A, C, D.

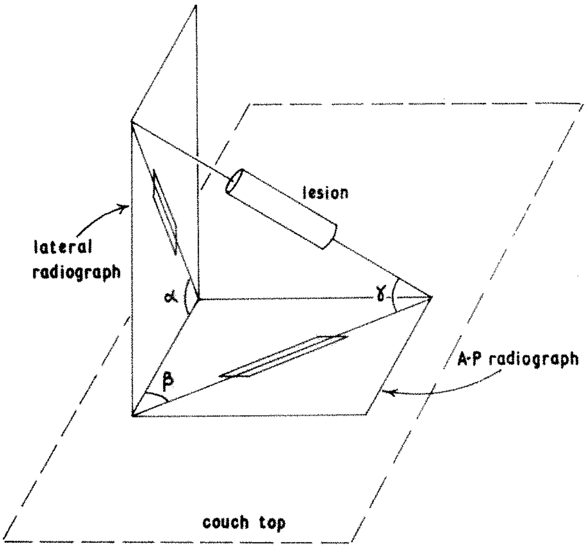

FIG. 2.
Lesion position relative to couch top (patient outline omitted for clarity).
(Angles α, β are lesion inclination in lateral and antero-posterior radiographs.)

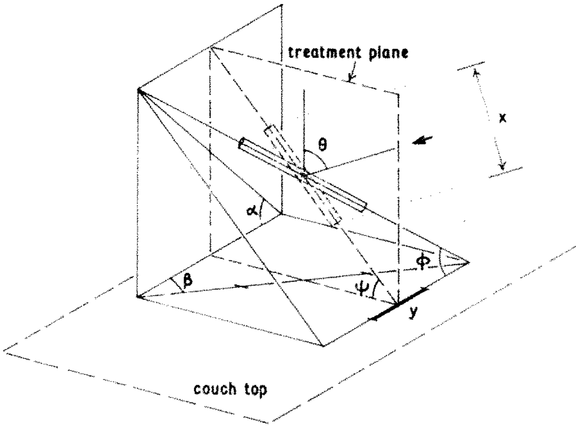

FIG. 3.
Lesion position relative to couch top, showing projection in treatment plane (Method 2).
Arrow shows direction of beam in treatment plane.

$$x = L \sin\phi \,.\, \cos(\theta - \psi)$$

Diaphragm twist D is therefore given by:

$$\tan D = \frac{x}{y} = \tan\phi \,.\, \cos(\theta - \psi)$$

From the geometry of Fig. 3, $\tan\psi = \dfrac{\tan\alpha}{\tan\beta}$, and $\tan\phi = \dfrac{\tan\beta}{\cos\psi}$

$\therefore \tan D = \tan\alpha \,.\, \sin\theta + \tan\beta \,.\, \cos\theta$

This is the general form of the equation: $\tan D = \tan\alpha \,.\, \sin\theta$, previously used in this department, for the situation where $\beta = 0$ (Buchan, 1969).

The treatment angle equations for Method 2 are therefore:

$$\left.\begin{array}{l} A = \theta \\ C = 0 \\ D = \arctan(\tan\alpha \,.\, \sin\theta + \tan\beta \,.\, \cos\theta) \end{array}\right\} \qquad (2)$$

In the conventional isodose chart the distribution is taken through the central axis, parallel to one side of the field, whereas the distribution required for dose summation in this treatment plane is angled across the beam by diaphragm twist D. The isodose line positions at the edge of the field in the treatment plane will therefore be more widely spaced than those of the normal field. If D is appreciable for a given field, use of normal isodose charts will introduce dosage errors at the edge of the lesion volume. This error may be corrected by expanding the relevant isodose chart perpendicular to the central axis (*i.e.*: moving the lateral positions of the isodose lines) by a factor of (sec D) to obtain an effective distribution slicing across the field.

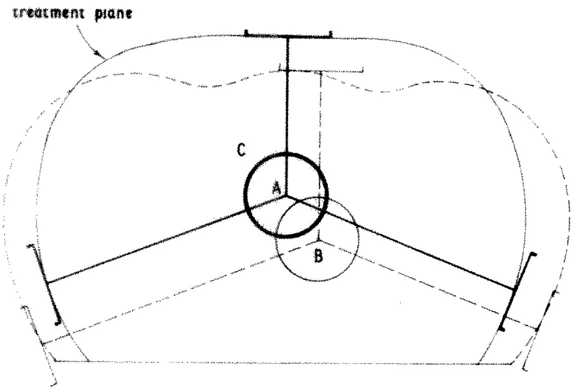

FIG. 4.
A three-field plan using Method 2.
(A) centre of lesion in treatment plane.
(B) one end of lesion in plane parallel to treatment plane.
(C) other end of lesion (contour not shown).

As with Method 1, missing tissue compensation will in general be necessary. However, as fields are arranged perpendicular to the principal patient axis, compensation may not be required in treatments where patient curvature perpendicular to the treatment plane is small. The dose uniformity along the length of the lesion should however be checked: *e.g.* by estimating the mid-lesion dose at the ends of the lesion. This may be done by obtaining patient contours in planes through the ends of the lesion, parallel to the treatment plane, and locating the lesion in each plane (see Fig. 4).

CHOICE OF METHOD

The choice of which method to use depends on clinical considerations such as lesion angle and patient curvature. Ideally, Method 1 is preferable in that the treatment plan is accurate, as each radiation field is perpendicular to the lesion axis. However the fields enter the patient obliquely resulting in a lower percentage depth dose at the lesion and more irradiation of healthy tissue. Method 2 is therefore often preferable, even though the treatment plan may be less accurate at the edge of the lesion due to effectively slicing across the normal isodose distributions. In Method 2 the patient set-up is easier as there is no couch twist.

It should also be noted that although derived for isocentric treatments, the equations also apply to fixed SSD treatments on isocentric machines. In addition, as there is no couch twist for Method 2, these equations may be used with other installations, such as vertically mounted units, if the head and diaphragms can be rotated.

REFERENCES

BESFORD, H., SIVYER, A., and BRAIN, E. W., 1964. A planning device for use with beam direction shells. *British Journal of Radiology*, *37*, 391–394.

BUCHAN, R. C. T., 1969. (Unpublished.)

FLEMING, J. S., and ORCHARD, P. G., 1974. Isocentric radiotherapy treatment planning where the treatment axis is not horizontal. *British Journal of Radiology*, *47*, 34–36.

Book review

Atlas of the Arteries of the Human Brain. By George Salamon, 2nd edn., 1973, pp. 189, £12.

The well-deserved success of the first edition of this atlas has stimulated Professor Salamon to give us a second edition within two years of its first appearance. The readers already familiar with the first edition will know that it gave a detailed account of the anatomy of the cerebral arteries and their branches. For this edition Professor Salamon has dotted the "i"s and crossed the "t"s, the main changes being in the detailed description of the middle and anterior cerebral cortical arteries. Many of the illustrations have been replaced by new and even better ones.

The form of the book is unchanged. It is based on a series of 430 brains in which the arteries had been injected and the specimens prepared by a method which is described in detail. Anatomical sections in three planes are each mounted next to a transparent radiograph of its vessels in such a way that the section and radiograph can be superimposed. This main section of the atlas is supplemented by a series of highly magnified angiographic sections showing the angioarchitecture of the cerebral cortex, central grey matter, brain stem and cerebellum. The book commences with a nicely illustrated history of the development of our knowledge of the cerebral circulation and a description of the course and distribution of each of the cerebral arteries, illustrated by selective injections.

The publishers have done justice to Professor Salamon's painstaking work, presenting it loose-leafed so that the plates can be more easily demonstrated but the atlas is robust and well bound. It is strongly recommended, not only to all those studying the neuro sciences, but also to students of anatomy. It is a perfect example of the great contributions that radiological methods can make to that subject.

B. KENDALL.

1976, *British Journal of Radiology*, *49*, 281–285 MARCH 1976

Case report

Radiographic and radioisotope evaluation of intra-osseous xanthoma

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The reports in the radiologic literature of osseous xanthomas are very rare, and only seven cases are found between 1947 and 1971. The following is an additional case with pathologic fracture of the tibia, where an intra-osseous xanthoma was diagnosed prior to occurrence of fracture. Radiographic and radioisotope studies were both instrumental in detecting the lesion six months before the fracture occurred.

CASE HISTORY

A 41-year-old, obese, black, male, steelmill worker was admitted in January 1974. Multiple, non-tender, hard, pedunculated and sessile nodules covered most of the body and extremities. He noticed the nodules first in 1954 and ever since the nodules interfered with his work, bruised easily and ulcerated.

On physical examination the nodules were seen covering hands, elbows, buttocks and knees (Fig. 1). Laboratory tests revealed serum cholesterol: 300 mg, triglycerides: 710 mg, and the rest of the tests being within normal limits. The blood glucose tolerance test showed slight elevation in

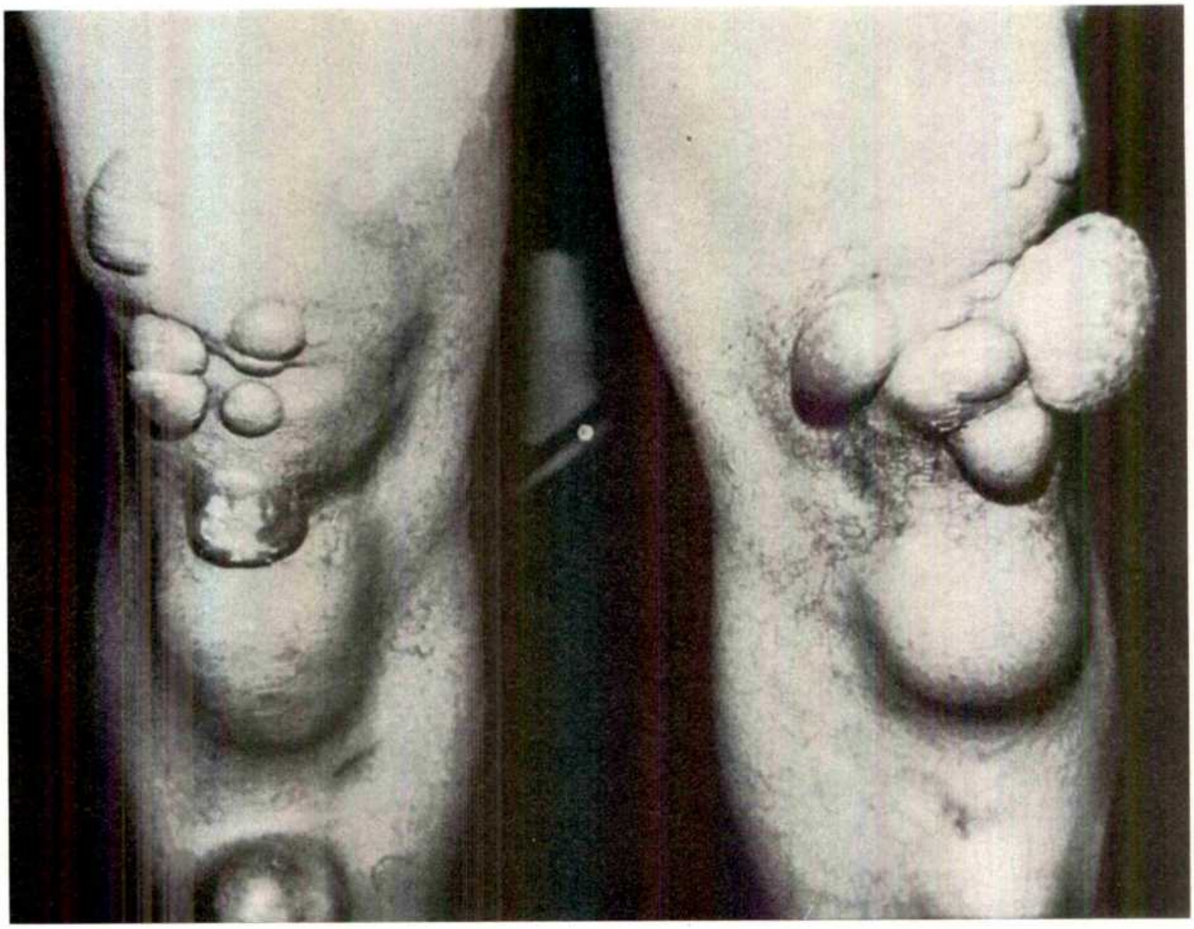

FIG. 1.

Both knees with nodular, tumour-like, well-outlined masses of different sizes. Note soft-tissue prominence in the areas of both tibial tuberosities.

the first two hours (142 mg/100 ml.) which decreased to normal limits at three hours. ECG showed findings compatible with left ventricular hypertrophy.

The chest X ray showed mild enlargement of the cardiac silhouette, and radiographic bone survey showed radiolucent bone lesion at the anterior aspect of the proximal right tibia with mild irregularity of the cortex at the area of the tibial tuberosity (Fig. 2). Some changes were also seen in the opposite tibia although to a lesser degree (Fig. 3). IVP and barium-contrast studies were unremarkable. Bone scan using ^{99}Tc^{m} polyphosphate showed increased uptake in the above-mentioned area of the right tibia, and to a somewhat lesser degree in the corresponding left tibia (Fig. 4). Liver scan using ^{99}Tc^{m} sulphur colloid showed generalized decrease of uptake in the liver. A liver biopsy showed mild to moderate fatty metamorphosis of the liver.

Surgical removal of several nodules showed these to be fixed and attached to tendon sheaths. On microscopic examination "numerous foam-laden macrophages with cholesterol clefts" were seen. Serum lipid and lipoprotein determination (Seidel-Wieland test) was positive for "floating" β-component. This was classified as Type III lipoprotein pattern with hypertriglyceridemia.

In August 1974 the patient was readmitted with a painful and swollen right knee and proximal right leg. This occurred following a fall.

Radiographic examination revealed a linear, radiolucent fracture line in the proximal right tibia through the abnormal area, noted on previous radiographs, confirming the diagnosis of an undisplaced pathological fracture (Fig. 5).

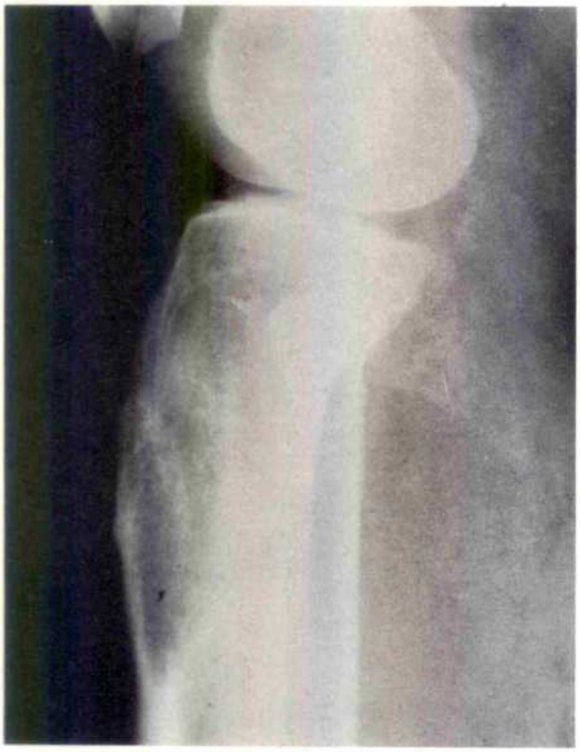

FIG. 2.

Lateral radiograph of right knee. Intra-osseous radiolucent lesion with sclerotic margins and mild endosteal reaction is seen in the proximal right tibia opposite the tibial tuberosity.

Craig needle biopsy of the lesion in the right tibia showed accumulation of lipoid material with typical foam-laden macrophages and cholesterol clefts. This confirmed the clinical diagnosis of intra-osseous xanthoma.

Follow-up film 70 days after the fracture showed healing and bony callus formation. The radiolucent lesion is still visible (Fig. 6).

DISCUSSION

The radiolucent lesion described in the anterior and proximal right tibia with sclerotic margins, preserved cortex of the bone and mild endosteal changes raised the suspicion of a slow-growing tumour.

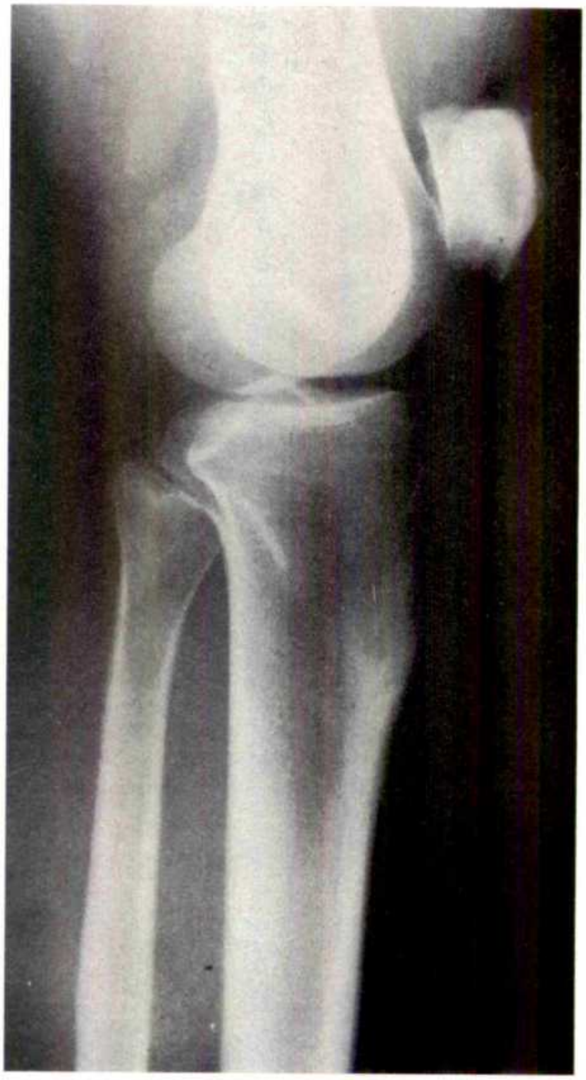

FIG. 3.

Lateral radiograph of left knee which shows small area of rarefaction and radiolucency, intra-osseous in position at the level of tibial tuberosity.

Due to the patient's xanthomatous skin lesions and an associated radiolucent bone lesion, intra-osseous xanthoma was considered first, and awareness of such a possibility may have precluded a pathological fracture.

Intra-osseous xanthomas are very rare and no specific guidelines for diagnosis are available at the present time.

Phenotyping of patients with primary hyperlipoproteinaemia is not within the scope of this writing and the reader is referred to works by Levy and Frederickson, 1968, Levy *et al.*, 1972, and Frederickson and Lees (1965) and the proceedings of the NIH conference published in *Annals of Internal Medicine* (Levy *et al.*, 1972). The main concern of this paper is to call attention to the diagnostic aspect of this rarely described entity. It is to be noted that each of the articles describing similar lesions is limited to only one case (Sneider 1963; Sorensen, 1964; Weintrob and Truswell, 1974). However, recent studies and present-day knowledge shows that a large number of the population will demonstrate high values of triglycerides and cholesterol even in the younger age group (Frederickson and Lees, 1965; Lees *et al.*, 1972). This is considered a familial and relatively common disorder and has an ever increasing interest in atherogenesis and coronary heart disease. The second consideration is that although cutaneous manifestations are rare, deposits within the tendon sheaths are not unusual.

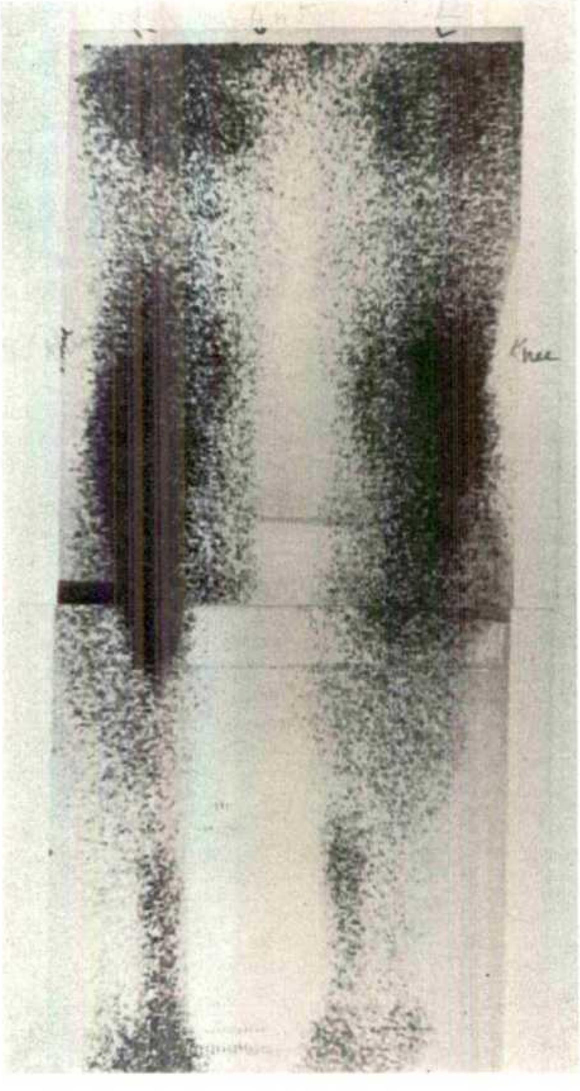

FIG. 4.

$^{99}Tc^{m}$-polyphosphate bone scan of both lower extremities with increased uptake in proximal portions of both tibiae, more prominent on the right side.

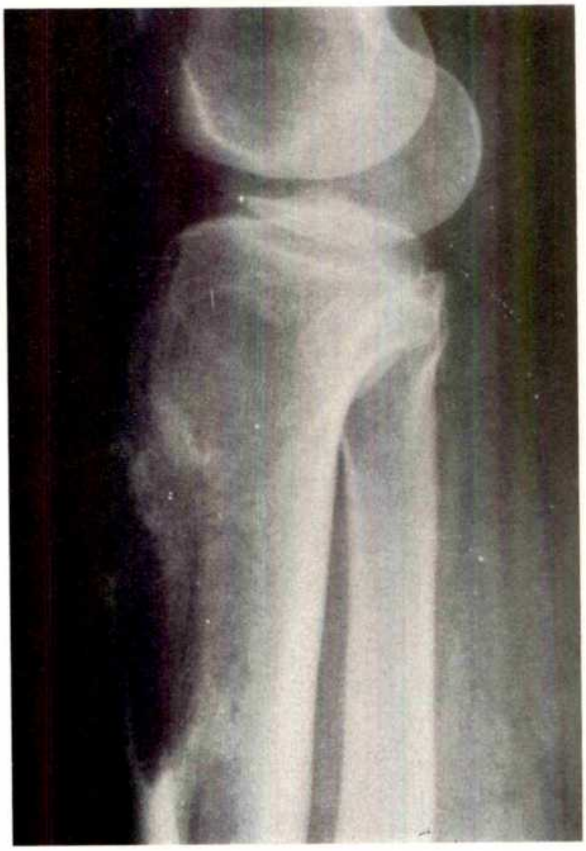

FIG. 5.

Lateral radiograph of right knee showing linear fractures through the radiolucent lesion.

Description of such cases is present in the literature (Blomqvist, 1962; March, Gilbert and Kain, 1957). Blankenhorn and Meyers (1969) describe a radiographic method for evaluation of xanthomatous involvement of Achilles tendon (Blankenhorn, 1969).

Thirdly, the fact that xanthomatous deposits in the tendon sheaths are not uncommon may predispose in certain cases to invasion by continuity and subsequent abnormal deposits within the bone of lipid rich material. Weintrob and Truswell (1974) report such findings in the hand of a patient with Type III hyperlipoproteinaemia, Sneider (1963) in the calcaneus, and in our case in the tuberosity of the tibia. However, other cases described (Brusco *et al.*, 1966; Koch and Lewis, 1956; Layani, Durupt and Lambert, 1958; Sorensen, 1964), fail to disclose relationship of osseous lesion and tendon sheaths.

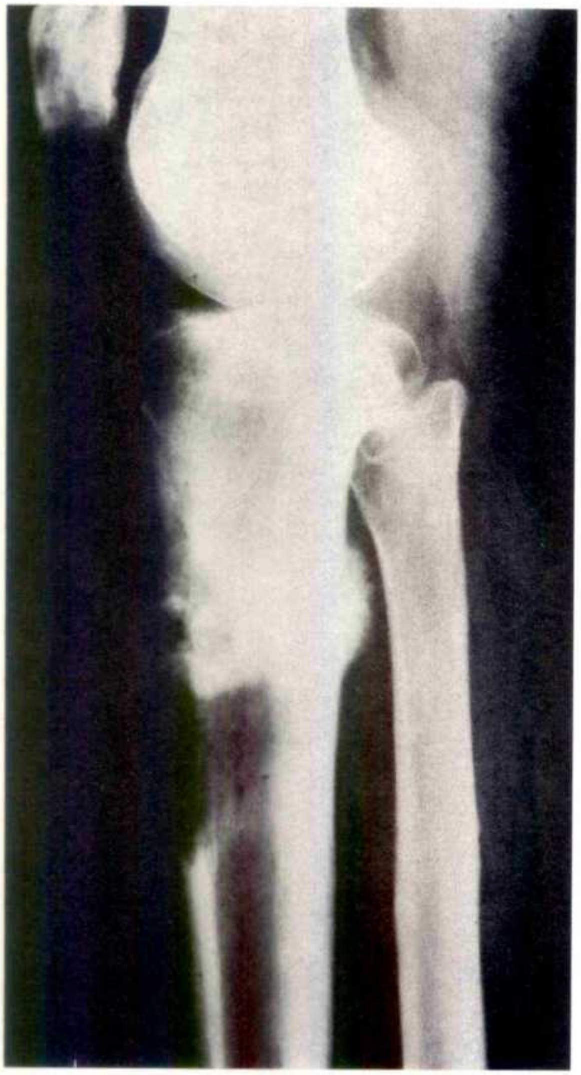

Fig. 6.

Lateral radiograph of right knee showing healing of fractures and bony callus formation.

Bone scanning with bone-seeking radiopharmaceuticals has improved considerably the perception of early bone lesions and, nowadays, $^{99}\text{Tc}^{m}$ labelled polyphosphate, diphosphonate and pyrophosphate are the most commonly-used agents. However, numerous conditions may show increased uptake and positive bone scan. The exact mechanism of their localization in bone is unknown, even though the uptake is influenced by the vascularity and the osteoblastic activity of the bone. In our patient with intra-osseous xanthoma, the right tibia showed a definite increase in uptake and the left tibia to a lesser degree. The amount of involvement generally correlated with the intensity of uptake and suggested an early lesion on the left side. We believe that this is the first intra-osseous xanthoma demonstrated by this method prior to pathological fracture.

SUMMARY

The value of early detection of intra-osseous xanthoma by radiologic and isotopic studies is demonstrated. Although we believed that the patient had only one lesion in the right tibia, discreet findings in the bone scan and inconclusive radiographic findings raised the possibility of another lesion in the opposite (left) tibia. This will encourage close follow-up studies of the left tibia to preclude the occurrence of pathological fracture in the future.

REFERENCES

Blankenhorn, D. H., and Meyers, H. I., 1969. Radiographic determination of Achilles tendon xanthoma size. *Metabolism*, *18*, 882–886.

Blomqvist, G., 1962. Xanthoma of tendo achillis. *Acta Radiologica*, *57*, 45–47.

Brusco, O. J., Howard, R. P., Jarman, J. B., and Furman, R. H., 1966. Osseous xanthomatosis and pathologic fractures in familial hyperlipemia (hyperglycidemia). *American Journal of Medicine*, *40*, 477–484.

Frederickson, D. S., and Lees, R. S., 1965. Editorial—A system for phenotyping hyperlipoproteinemia. *Circulation*, *XXXI*, 321–327.

Koch, H. J., jun., and Lewis, J. S., 1956. Hyperlipemic xanthomatosis with associated osseous granuloma. *New England Journal of Medicine*, *255*, 387–389.

Layani, F., Durupt, L., and Lambert, P., 1958. Etude critique des xanthomatoses osseuses. *Semaine Hôpital, Paris*, *34*, 3041–3053.

Levy, R. I., and Frederickson, D. S., 1968. Diagnosis and management of hyperlipoproteinemia. *American Journal of Cardiology*, *22*, 576–583.

LEVY, R. I., FREDERICKSON, D. S., SHULMAN, R., BILHEIMER, D. W., BRESLOW, J. L., STONE, N. J., LUX, S. E., SLOAN, H. R., KRAUSS, R. M., and HERBERT, P. N., 1972. Dietary and drug treatment of primary hyperlipoproteinemia, NIH Conference. *Annals of Internal Medicine, 77,* 267–294.

MARCH, H. C., GILBERT, P. D., and KAIN, T. M., 1957. Hypercholesterolemic xanthomata of the tendons. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 77,* 109–114.

SNEIDER, P., 1963. Xanthoma of the calcaneus. *British Journal of Radiology, 36,* 222–223.

SORENSEN, E. W., 1964. A report of an unusual case complicated by bone lesions, macrocytic anemia and leukemoid bone marrow, *Acta Medica Scandinavica, 175,* 207–214.

WEINTROB, L., and TRUSWELL, A. S., 1974. A case of type III hyperliproproteinemia with xanthomata. *British Journal of Radiology, 44,* 215–218.

Book reviews

An Atlas of Radiation Histopathology. By D. C. White, pp. iv+227, 1975 (Washington, U.S. Energy Research and Development Administration), $10·10.

The U.S. Armed Forces Institute of Pathology is reputed to hold the largest collection of human histopathological material in the world, and publications emanating from the Institute reflect the outstanding provisions of their source. This inexpensive paperback by the Chief of the Institute's Division of Radiation Pathology follows that tradition. The first of the 12 chapters occupies one-third of the book, and is devoted to the effects of whole-body irradiation in relation to the kinetics of the different tissues as they affect the expression of radiation damage. This chapter draws on rare clinical material obtained from five subjects who had been accidentally exposed to whole-body doses of between 600 and 8,000 rads of radiation of mixed quality. The remaining chapters are divided by their reference to the various organs of the body; each outlines the relevant structure and function of the organ, the clinical effects of radiation damage to it, and the histological appearance of such damage. The material is drawn almost entirely from radiotherapy cases.

The matter is illustrated in black and white by over 200 photomicrographs and almost 30 excellent helpful drawings. A deficiency of the full legends to the photomicrographs is that they never give the magnification and seldom indicate the time since irradiation; also, several of the low power views show too little detail to be informative, the reader having difficulty in distinguishing unstructured radiation damage from insufficient resolution.

It is a considerable achievement to collect together so wide a range of material almost exclusively from clinical sources; the opportunities for obtaining specimens, especially those which illustrate sequential changes following irradiation, are inevitably restricted; as might be expected, late changes predominate in the illustrations. Thus, the atlas may be a unique work for those whose need is for reference to specifically clinical material. The student of principles will find the first chapter of particular value; the dependance of expression of radiation damage on tissue cell kinetics is well and fully described. The author's assurance that an index is rendered unnecessary by the systematic division of the chapters is entirely acceptable.

H. B. HEWITT.

Tumours of the Nervous System, Edited by H. Gunter Seydel, pp. x+193, 1975 (John Wiley and Sons), £10.00.

This publication is an account of the proceedings of the Annual Cancer Symposium held at the Fox Chase Cancer Centre.

There is a section covering the use of radionuclides in the diagnosis of tumours of the CNS. This firstly covers scanning procedures and is well illustrated in black and white. There is an interesting comparison of the accuracy of various neurodiagnostic procedures and also the success rate of brain scanning in specific tumours. There then follows an interesting section dealing with dynamic function studies using isotopes in the blood stream and also introduced into the cerebro-spinal fluid. This section then closes after considering the use of radio-isotopes in the localization of intraocular and orbital tumours.

The rest of the book is concerned with the treatment of tumours in the CNS. There are papers on the surgical approach to the treatment of gliomas, the treatment of glioblastoma multiforme in different ways and combinations of surgery, radiotherapy, chemotherapy and radiation in the induced hyperthyroid state. Hyperbaric oxygen and radiation therapy for malignant gliomas is considered and the results of a pilot study reported. There is a paper considering the present state of the chemotherapy of brain tumours in childhood.

The pituitary receives a good deal of attention. There is an excellent and detailed account of the treatment of pituitary tumours by radiotherapy. This is followed by a very informative account of radiation therapy in acromegaly and non-secretory chromophobe adenomas.

The role of cryosurgery in the treatment of acromegaly is considered and there then follows a paper on the use of Bragg peak proton therapy to produce hypophysectomy. This is a detailed and interesting account. Finally there is a paper concerning the treatment of metastic disease of the nervous system by radiation therapy. This is a detailed analysis of what can be achieved when treating various metastases in different sites.

This account of the symposium is a very worthwhile addition to the library of anyone concerned with the investigation or management of tumours of the nervous system.

B. T. HALE.

1976, *British Journal of Radiology*, *49*, 286–293

Proceedings of The British Institute of Radiology*

Abstracts of papers read at the Joint Radiological Meeting held at Nottingham University Science Block, on September 27–28, 1974

Joint Scientific Session

Bone-seeking isotopes—pharmacology and mechanisms of uptake, by M. Frier and P. A. Griffiths.
The role of radio-isotopes in the study of hyperparathyroidism, by D. J. Hosking.
Pre-operative localization of enlarged parathyroid glands by means of venous sampling, by G. A. P. In der Maur and S. A. Duursma. (No abstract received)
Photographic harmonization as a means of image enhancement in the study of bone lesions, by B. S. Worthington.
Critical appraisal of scan minification, by R. Potter and P. A. Griffiths.

Diagnostic Session

An evaluation of fetal cephalometry, by P. Davies.
Echocardiography in the general hospital, by P. G. Small.
Contrast media in knee arthrography, by E. J. Roebuck.
Shoulder arthrography, by B. J. Preston and J. P. Jackson.
Adenomyomatosis of the gall-bladder, by D. R. Knapp. (No abstract received)
Multi-colour transformation of the conventional angiogram and its applications, by B. S. Worthington.
Why enteroclysis of the small intestine?, by J. L. Sellink.
A radiological study of morphology and growth in the human fetal colon, by P. F. Harris, P. R. M. Jones and C. S. Robertson.
Detection of spread in carcinomas of the female genital tract, by H. Ngan.
The nephrogram, by P. Davies.

Therapy Session

Clinical significance of carcino-embryonic antigen, by A. M. Mackay.
The MEM test in the diagnosis and prognosis of malignant disease, by J. A. Pritchard.
Protein analysis in the diagnosis and monitoring of myeloma and macroglobulinaemia, by P. M. Carter.
Urinary hydroxyproline excretion in the monitoring of carcinoma of the breast, by Eva Lester.
Monitoring of neuroblastoma, by Jane V. Bond.
Electron spin resonance as a technique for monitoring activity and response to therapy in malignant diseases, by M. A. Foster.
Monitoring of choriocarcinoma, by K. D. Bagshawe and P. A. M. Walden
Report on treatment of cancer of the ovaries, by Tj. Kuipers.
Advances in treatment of malignant disease in children, by Dorothy Pearson.

BONE-SEEKING ISOTOPES—PHARMACOLOGY AND MECHANISMS OF UPTAKE

By M. Frier and P. A. Griffiths

Department of Medical Physics
Nottingham General Hospital

The general properties of bone-seeking isotopes and the pharmacological properties of ^{18}F and ^{99}Tc^{m} phosphate complexes in particular are reviewed. Data were presented on:

(1) The chemical state of cyclotron-produced fluorine. It is concluded that fluorine exists as a simple ionic species.
(2) The rate of uptake of fluorine and aluminium—fluorine complex in rat bone. The uptake has been measured at several time intervals up to two hours in rat femur, pelvis and sternum. The same rate of uptake was observed in all the bones, and marked similarity between the rates of uptake of ionic fluorine and complexed fluorine was observed. This result markedly differs from published data (Kraus *et al.*, 1968; Chaudri, Gartside and Ramicar, 1970). The limited data available (Yano *et al.*, 1973) on the rate of uptake of technetium-labelled diphosphonate in rat femur is superimposable on the present data.

The data suggests that a common rate-determining step exists for the uptake of all bone-seeking isotopes, regardless of their chemical state. This probably involves transfer from the body fluids into the hydration shell of the bone surface. The exchange process with the bone which follows undoubtedly differs depending upon the chemical state, but all exchange processes appear faster than the initial transfer step.

REFERENCES

Chaudri, M. A. Gartside, J. M., and Ramicar, A., 1970. The chemical form of cyclotron-produced ^{18}F used in bone scintigraphy. *British Journal of Radiology*, *43*, 534–536.
Kraus, O., Maier-Borst, W., Sinn, H., Lorenz, W. J., Prpić, B., Harbst, H., 1968. *Jahrestagung der Gesellschaft für Nuclearmedizin*, pp. 339–343 (Wiesbaden).
Yano, Y., McRae, J., Van Dyke, D. C., and Anger, H. O., 1973. *Journal of Nuclear Medicine*, *14*, 73.

THE ROLE OF RADIO-ISOTOPES IN THE STUDY OF HYPERPARATHYROIDISM

By D. J. Hosking

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Changes in bone mineral content have been studied in hyperparathyroidism using *in vivo* activation analysis or photon absorptiometry. In general, normal skeletal radiographs imply a loss of less than 15 per cent of bone mineral, while mineral content in those with abnormal radiographs is reduced by 15–45 per cent.

Operative treatment is likely to be advised in most cases of hyperparathyroidism, but there are some patients who may wish to defer or refuse operation. In these latter circumstances sequential measurements of bone-mineral content may help in the conservative management of these cases. Progressive demineralization which may occur in the untreated situation can be demonstrated to regress following parathyroidectomy.

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*Reprints available from the Editorial Office.

Combination of measurements of skeletal mineral with isotopic tests of calcium absorption provide a more complete picture of patho-physiology without involving the need for hospitalization. Absorption is increased in most cases of hyperparathyroidism, except those with overt bone disease where it has decreased, although there seems to be little correlation between calcium absorption and the severity of bone disease. There is, however, a much stronger direct correlation between urinary calcium excretion and the severity of demineralization. This illustrates the important homeostatic role of the kidney in modifying the hypercalcaemia of hyperparathyroidism.

PRE-OPERATIVE LOCALIZATION OF ENLARGED PARATHYROID GLANDS BY MEANS OF VENOUS SAMPLING

By G. A. P. In der Maur and S. A. Duursma

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(No abstract received).

PHOTOGRAPHIC HARMONIZATION AS A MEANS OF IMAGE ENHANCEMENT IN THE STUDY OF BONE LESIONS

By B. S. Worthington

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Photographic harmonization refers to a transformation of the radiographic image, whereby the background or "macro-contrast" is reduced, while that of the fine detail is preserved. A blurred positive mask of a radiographic image is produced by diffusing its image through a thin sheet of opal Perspex. The original film and this mask are then combined, with the result that in the final harmonized copy part of the background is subtracted out with resulting subjective enhancement of fine detail. Combining the harmonized film with the original restores background contrast to normal, while detail contrast is much improved.

In addition, areas of high density in the original film fall within the useful tonal range of the harmonized film, which allows better deliniation of soft-tissue shadows.

CRITICAL APPRAISAL OF SCAN MINIFICATION

By R. Potter and P. A. Griffiths

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To investigate the effect of scan minification on the perceptibility of defects in radioisotope distributions, a series of scans was obtained of a uniform phantom with various spherical cold defects. The defects were positioned in five different arrays, each one being scanned at a series of information densities ranging from 100 to 1,600 cm^{-2} on two different scanners (Ohio Nuclear 84 and Selo DS7). Full size and 2:1 minified images were assessed by three observers independently under controlled conditions on five different occasions.

The results indicate a marginal improvement in the detectability of the smaller lesions. However, the claim that scanning speeds may be doubled when reducing size of image by a factor of 2 is disputed since a significant loss of detectability occurs in small defects and defects out of focus.

AN EVALUATION OF FETAL CEPHALOMETRY

By P. Davies

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An improved method of fetal cephalometry by ultrasound was described. It involves a search procedure which was illustrated by a flow chart and a checking procedure (the cephalic diameter is checked in a plane at right-angles to that in which it was estimated). Experiments have shown that there is no significant difference between measurements made on different machines, provided that the assumed speed of ultrasound in tissue is the same for both machines. Serial cephalometry may be performed by different observers with no loss of accuracy. The chief source of variation is the failure to measure the same diameter on each occasion. The term "fetal cephalic diameter" should be substituted for the term "fetal bi-parietal diameter" when referring to the procedure of ultrasonic cephalometry.

ECHOCARDIOGRAPHY IN THE GENERAL HOSPITAL

By P. G. Small

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The paper was concerned with stressing the importance of this investigation in the general hospital, remote from sophisticated cardiovascular facilities. The widespread acquisition of obstetric-type B-scan machines should make it possible for this examination to be carried out on a far wider scale. The paper emphasizes the more useful applications of this technique, which can be performed after relatively little practice, and describes the results obtained over a two-year period.

A series of examples of typical scans were demonstrated, and the correlation with the physical signs of mitral stenosis illustrated. The importance of close co-operation with the cardiologists was stressed. Some reference was also made to those less common conditions which are likely to be encountered and can be diagnosed reliably by ultrasound.

The involvement of radiologists in this rapidly-growing technique is strongly encouraged.

CONTRAST MEDIA IN KNEE ARTHROGRAPHY

By E. J. Roebuck

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A short review of development of techniques in knee arthrography was given together with a short account of the author's technique. Experiences using Dimer X as a positive contrast medium were compared with those in a controlled group of patients who were examined using Urografin 60 per cent. It was shown that Dimer X has advantages both with regard to radiographic quality and to the minimal side effects which were encountered. It was concluded that Dimer X is the positive contrast media of choice at the present time.

Proceedings of The British Institute of Radiology

SHOULDER ARTHROGRAPHY

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Pain and limitation of movement at the shoulder joint are common presenting complaints, and clinical examination and routine radiography do not usually determine the exact cause of the patient's symptoms. Arthrography is a method of investigating shoulder disability, and our experiences based on 42 examinations are presented.

The average age of the patients was 53 years, and three times as many males as females underwent the procedure. A history of trauma could be elicited in approximately 60 per cent of cases.

Routine antero-posterior radiographs in internal and external rotation, an erect antero-posterior film, axial views of the shoulder and intertubercular groove are taken. With the patient supine, a short bevelled needle is inserted into the shoulder by anterior approach. 1 ml. of Conray 280 is injected under screen control to confirm that a satisfactory puncture has been made and then 12 ml. of Conray 280 followed by 10 ml. of filtered air are injected under screen control. The needle is removed, and following careful manipulation of the shoulder, a further set of films is obtained. The only complications encountered were discomfort and pain. All patients had mild discomfort during the procedure and for about two hours afterwards. The features of a normal air-contrast arthrogram were described.

The main abnormal arthrographic patterns which were recognized are as follows:

(1) complete tear of the rotator cuff;
(2) incomplete tear of the rotator cuff;
(3) capsulitis.

Complete tears are revealed by the passage of contrast from the glenohumeral joint into the subacromial bursa, and some idea of the size of the tear may be obtained from observing the rate of filling of the subacromial bursa on the screen as the contrast is injected, and by noting the radiolucent band between the subacromial bursa and contrast overlying the upper humerus, as this area represents the rotator cuff. Incomplete tears were recorded in only two cases, and the radiographic diagnosis is based on the passage of contrast from the glenohumeral joint into the rotator cuff and the absence of filling of the subacromial bursa.

Contracture of the synovial pouches, in particular the axillary and subscapularis, is the main arthrographic feature of capsulitis, and in this condition, the joint only accepts smaller amounts of fluid. It was diagnosed in eight cases.

The bicipital tendon sheath abnormalities that were detected were:

(1) non-filling, and
(2) leakage of contrast.

Subluxation and dislocation of the bicipital tendon was not recorded.

In two cases there was an enlarged entrance to the subscapularis bursa, and this has been recorded by Reeves (1966) in recurrent anterior dislocation of the shoulder, but our patients had not sustained such an injury.

The technical problems of shoulder arthrography are:

(1) failure to puncture the joint;
(2) periarticular injection of contrast;
(3) delayed filling of the subacromial bursa;
(4) injection of contrast into subacromial bursa;
(5) mistaking biceps tendon sheath for subacromial bursa.

Over 25 per cent of our cases had their shoulders explored, and the arthrographic findings were confirmed on all occasions. In four of our cases, the patients had persistent shoulder disability although the arthrograms were normal. It was thought possible that a deep central tear of the rotator cuff or a healed partial or complete tear of the rotator cuff leaving a fibrous nodule or an undetected bicipital tendon lesion could be responsible for these symptoms, but in two of these cases, the shoulders were explored and no abnormality was seen.

It is concluded that shoulder arthrography is an accurate method of giving further information concerning lesions of the shoulder joint.

ADENOMYOMATOSIS OF THE GALL-BLADDER

By D. R. Knapp

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(No abstract received).

MULTI-COLOUR TRANSFORMATION OF THE CONVENTIONAL ANGIOGRAM AND ITS APPLICATIONS

By B. S. Worthington

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Diagnostic radiology is dominated by image representation in black and white separated by a tonal range of varying shades of grey. Application of colour to radiographic images must be clearly related to meaningful anatomical units such as blood vessels rather than physical abstractions from the black and white image.

By photographing each of three films from an angiographic series through a different colour filter on to a single frame of colour film, the vascular anatomy in the composite image is rendered in lines of changing hue. Kodak Wratten filters in the additive primary colours, red, green and blue are used. When positive subtraction prints of the same films are photographed through the same filters, the image structure is built up in the subtractive primary colours. Where there is overlap between the selected phases, vessels common to two or all the films will appear in compound colours. For three overlapping phases with normograde flow, coloured respectively red, green and blue the contrast in the final image will follow a change in hue moving from one colour to another further on in the sequence red–yellow–green–cyan–blue.

The practical value of multicolour imaging derives from the clear display of the topographical relationship of vessels in the three component films, and in addition, because the movement of contrast through the vessels is reflected in predictable succession of colour shifts, it becomes possible to examine relative differences in the rate of transit of contrast through different groups of vessels.

WHY ENTEROCLYSIS OF THE SMALL INTESTINE?

By J. L. Sellink

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It is easier to demonstrate anatomical and functional abnormalities of the small intestine when the loops are well-filled with contrast fluid, and the examination, like that of the colon, is carried out under fluoroscopic control. The length of the examination must therefore be very short, and the contrast fluid may not flocculate since in that case evaluation of the anatomy of the mucosa is of course completely impossible. Under normal conditions the rate of transit through the small intestine is dependent upon the degree of filling of the duodenum and the proximal jejunum, and therefore the rate of gastric emptying rather than on factors in the small intestine itself.

A short examination, a sufficient degree of filling of the intestinal loops, prevention of flocculation and evaluation of the motility of the small intestine, which are comparable, are all realized if the contrast fluid is not administered as a drink but by means of an infusion directly into the duodenum. Because an infusion is used, the course of the examination can be controlled completely and, if desired, good double-contrast films of the small intestine can also be made.

The enteroclysis examination is, however, only successful if a number of technical requirements are satisfied; these were discussed briefly.

A RADIOLOGICAL STUDY OF MORPHOLOGY AND GROWTH IN THE HUMAN FETAL COLON

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Radiographic studies were made of the opacified colon in six human fetuses between 11 and 20 weeks gestation. The studies included:

(1) general morphology;
(2) measurements of total colon length and of its pre-splenic (proximal) and post-splenic (distal) parts;
(3) changes in the two-dimensional (vertical and transverse) position of the splenic flexure and ileo-caecal junction.

The changes in vertical position were compared with longitudinal somatic growth using the position of T10 vertebra as a reference point.

Morphologically, the colon proximal to the splenic flexure can be classified into three types—transverse, oblique and ascending/transverse. Although the transverse type predominates in the younger fetuses, and the ascending/transverse in the older, the three types overlap considerably in their incidence in relation to maturity.

The relationship between total colon length and crown-rump length is rectilinear. However, growth of the distal colon (primitive hind-gut) is distinctly greater ($\times 1 \cdot 4$) than that of the proximal colon. The splenic flexure and ileo-caecal junction both grow in a cranial direction but at differing rates, the splenic flexure being faster and comparable with T10 (*i.e.*, general somatic growth). Splenic flexure and ileo-caecal junction both migrate away from the midline during fetal growth.

These findings challenge the conventional description of the caecum descending to the right iliac fossa from a subhepatic position. This would require more rapid growth in the proximal than in the distal colon. In fact growth is more rapid in the distal colon and causes the splenic flexure to grow more cranialwards than the ileo-caecal junction, the two points becoming progressively further apart and causing the proximal colon to change from a transverse to an oblique form. The adult (ascending/transverse) form of colon depends on early adhesion between the mid-point of the proximal colon and the second part of the duodenum otherwise the oblique form of proximal colon persists.

DETECTION OF SPREAD IN CARCINOMAS OF THE FEMALE GENITAL TRACT

By H. Ngan

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Forty-two female patients with a known carcinoma of the genital tract were studied because of symptoms suggestive of recurrence. Combined bilateral pedal lymphogram and intravenous urogram were performed on the majority of these patients. Bilateral venograms were also carried out in selected cases. It was found that lymphatic obstruction, the presence of filling defects in opacified lymph-nodes, non-opacification of lymph-nodes in expected sites, compression or obstruction of the iliac veins and inferior vena cava, displacement of the ureters or bladder and ureteric obstruction were features which indicated recurrence. Of the 29 patients with spread of the tumour to the pelvic and/or para-aortic lymph nodes, 18 have since died. Of the 13 patients who were free of disease in the pelvic and para-aortic lymph-nodes, all but one are alive and well. It is concluded that leg oedema, pain and the presence of an abdominal mass are features which suggest that there may be recurrence of the tumour. Furthermore, the prognosis in those patients who have radiological evidence of spread of the tumour to the pelvic and/or para-aortic lymph-nodes is extremely grave.

THE NEPHROGRAM

By P. Davies

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The nephrogram has been studied for many years. Early studies showed that a 70 per cent contrast medium rapidly injected through a large bore needle outlined the renal arteries and renal parenchyma. Modern contrast media, disposable plastic syringes and large bore needles allow a nephrogram to be obtained in every case. The author's technique is to inject 50 ml. of Conray 420 in less than 30 seconds after which a film is exposed at a minute from the start of injection. This is an adequate dose. If the film is unsatisfactory, the fault can be remedied and a second injection given. Tomography is used if the renal areas are obscured and in cases of renal failure. The urogram must be tailored to solve the clinical problem on the first occasion the patient attends. It is important, especially in renal failure, to relate the appearances to those that have been described rather than to rely on theoretical predictions. Various forms of nephrogram can be distinguished; these are best referred to as being anatomical or descriptive terms such as cortical, medullar, diffuse, soap bubble or striated, etc. The evolution of the nephrogram is important in differentiating various conditions, especially acute calculous obstruction. The early nephrogram film at a minute after the start of injection is indicated in all cases.

CLINICAL SIGNIFICANCE OF CARCINO-EMBRYONIC ANTIGEN

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The radio-immunoassay of plasma carcino-embryonic antigen (CEA) has been undertaken in many patients with a wide variety of neoplastic and non-neoplastic disorders. In general, the highest levels are found in patients with gut-derived carcinomas, and are dependent on the extent of disease, although the plasma CEA is not always raised even if tumour is disseminated. However, there is an overlap between the values found in patients with early or localized tumours, and patients with inflammatory or regenerative conditions (*e.g.* hepatitis, ulcerative colitis, bronchitis). As a screening procedure to detect early carcinoma, as a method of localizing the site of origin of the tumour, or as a means of distinguishing neoplastic and non-neoplastic conditions the CEA test has little value. However, in individual patients the initial level may be of prognostic significance and serial assays showing a steady increase may indicate metastatic disease before it is possible to detect it by other routine methods. This is particularly true of colonic carcinoma. It is also possible that the test may be used to monitor treatment. Therefore the test would seem to be of definite but limited value in the assessment of some aspects of the management of malignant disease.

THE MEM TEST IN THE DIAGNOSIS AND PROGNOSIS OF MALIGNANT DISEASE

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An *in vitro* test for the detection of malignant disease as reported by Field and Caspary (1970) was confirmed (Pritchard *et al.*, 1972). The positivity of a result in the MEM test can be elevated by an increase in the number of test lymphocytes or by an increased radiation dose to the guinea-pig peritoneal exudate. An enhanced separation of MEM results from "control" and cancer subjects was obtained by adopting a split incubation régime: The MOD-MEM test.

Preliminary results suggest that the MOD-MEM test may be of value in assessing immunological compatibility. Results of the MOD-MEM test in non-malignant disease indicated that specificity for cancer was not maintained. Degenerative disease with possible nerve-tissue involvement produced results within the cancer range. Of 115 cases studied, 13 non-cancer subjects gave positive results where sensitization could not be attributed to a specific cause. One of these cases has presented with clinically-diagnosed malignant disease six months after the original test.

The MOD-MEM test may be of value in indicating the presence of tumour, providing localizing symptoms are present. Clinical evidence suggests that the test in its present form has little value as a prognostic test since the result from "positive" subjects does not vary before, during or after treatment, whether surgical or radiotherapy mediated.

REFERENCES

Field, E. J. and Caspary, E. A. 1970. Lymphocyte synthesization: an *in vitro* test for cancer. *Lancet*, *2*, 1337.

Pritchard, J. A. V., Moore, J. L., Sutherland, W. H., and Joslin, C. A. F., 1972. Macrophage-electrophroetic-mobility (MEM) test for malignant disease, *Lancet*, *2*, 627.

PROTEIN ANALYSIS IN THE DIAGNOSIS AND MONITORING OF MYELOMA AND MACROGLOBULINAEMIA

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The average survival of patients with myelomatosis has greatly increased over the last 15 years due to better general management and to the introduction of alkylating agents and biochemical monitoring. Most plasmacytomata synthesize monoclonal proteins, and the detection of these proteins in serum and urine aids diagnosis and enables tumour monitoring.

The synthesis of paraprotein by myeloma cells is fairly constant: for IgG it is $0{\cdot}5 \times 10^{-11} - 3{\cdot}4 \times 10^{-11}$ g/myeloma cell/day (Salmon and Smith, 1970). Since paraprotein half-life can be calculated from the serum concentration (in Schultze and Heremans, 1966), total paraprotein synthesis can be calculated, allowing estimations to be made of tumour mass. Using serum paraprotein concentrations as reflections of tumour size, tumour growth and regression may be monitored (Hobbs, 1971).

A good response to treatment is a 10–100-fold reduction in tumour size (Salmon, 1973), and estimations of paraprotein levels and Bence-Jones proteinuria during treatment enable assessment of response. Many patients who initially respond, however, later relapse and alterations in paraprotein levels may both precede clinical changes and also show the nature of the tumour escape (Hobbs, 1971).

There are now available very many techniques of greater sensitivity for the detection of monoclonal proteins. It is by the application of these techniques that monitoring of plasmacytomata will develop further.

REFERENCES

Hobbs, J. R., 1971. Immunocytoma o' mice and men. *British Medical Journal*, *2*, 67–72.

Salmon, S. E., 1973. Immunoglobulin synthesis and tumour kinetics of multiple myeloma. *Seminars in Haematology*, *10*, 135–147.

Salmon, S. E., and Smith, B. A., 1970. Immunoglobulin synthesis and total body tumour cell number in IgG multiple myeloma. *The Journal of Clinical Investigation*, *49*, 1114–1121.

Schultze, H. E., and Heremans, J. F., 1966. *Molecular biology of human proteins* (Elsevier Publishing Company, Amsterdam).

URINARY HYDROXYPROLINE EXCRETION IN THE MONITORING OF CARCINOMA OF THE BREAST

By Eva Lester

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Urinary hydroxyproline excretion is a measure of collagen turnover, and is known to be increased in primary or secondary bone tumours. In advanced breast cancer with radiologically demonstrable metastases urinary hydroxyproline excretion is almost always increased. It is also increased in some patients without radiologically demonstrated metastases. A long-term prospective study to compare the sensitivity of urinary hydroxyproline excretion, standard X ray and radiographs and radioisotope bone scanning in detecting those patients with carcinoma of the breast who already have metastatic bone disease at the time when they first present is in progress.

MONITORING OF NEUROBLASTOMA

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Neuroblastoma is already a systemic disease in the majority of children by the time the diagnosis is made, and it is important that patients are fully investigated to assess the degree of spread before treatment is started. A full X-ray skeletal survey with adequate views of the skull together with bone-marrow biopsy and measurement of urinary vanillylmandelic acid (VMA) should be carried out initially. If possible a whole-body bone scan and full analysis of catecholamine excretion should also be done.

The staging system of D'Angio and Evans (1971) is particularly useful since this puts into a separate category those infants with a primary tumour with a particular pattern of metastases to liver, skin and bone marrow associated with a good prognosis and requiring minimal treatment to initiate regression of disease.

A raised level of urinary VMA is the most constant metabolic abnormality in patients with neuroblastoma and serial measurements provide a reliable method of assessing response to treatment (Liebner and Rosenthal, 1973). In those patients who survive free of disease the VMA promptly returns to normal following treatment, whereas in those patients whose disease persists the VMA remains raised.

The main sites of metastases in neuroblastoma are the bones and bone marrow. Repeat skeletal survey and bone-marrow biopsy should be done in the follow-up of treated patients.

Disease-free survival remains less than 30 per cent, and if new methods of treatment are to be fully assessed, careful monitoring of both the metabolic activity of the tumour and its degree of metastatic spread are important.

REFERENCES

D'Angio, G. J., Evans, A. E., and Koop, C. E., 1971. Special pattern of widespread neuroblastoma with a favourable prognosis. *The Lancet*, *1*, 1046–1049.

Liebner, E. J., and Rosenthal, I. M., 1973. Serial catecholamines in the radiation management of children with neuroblastoma. *Cancer*, *32*, 623–633.

ELECTRON SPIN RESONANCE AS A TECHNIQUE FOR MONITORING ACTIVITY AND RESPONSE TO THERAPY IN MALIGNANT DISEASES

By Miss M. A. Foster

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Samples of whole blood have been collected from patients suffering from several types of malignant disease. ESR signals were observed in these, and in blood of normal controls. These signals appear to arise from transferrin ($g \sim 4{\cdot}2$) and from caeruloplasmin ($g = 2{\cdot}049$).

It was found that there was little alteration in size of either signal in cases of breast cancer or of squamous cell carcinoma. In both these types of malignancy, non-specific response to treatment could be observed. Patients suffering from Hodgkin's disease showed definite patterns of change of signal size. During the inactive phase of the disease, the signals were almost undistinguishable from those of controls; but during active phase the size of the 2·049 signal was elevated by over 100 per cent and the 4·2 signal decreased in size. Such changes were less pronounced for the other lymphomas. Size of 2·049 signal appears to be an indicator of the effectiveness of therapy, and there is some evidence that the increase in size of the 2·049 signal precedes other signs of increasing activity in Hodgkin's disease.

MONITORING OF CHORIOCARCINOMA

By K. D. Bagshawe and P. A. M. Walden

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Trophoblastic tumours encompass a spectrum of disease from the relatively benign hydatidiform mole through invasive mole to the highly malignant tumour, choriocarcinoma. They possess certain unique features which set them apart from other forms of malignant disease. Since the trophoblast is a fetal tissue it contains a genetic contribution from the male parent and hence these tumours are allografts generally occurring only in the maternal host. They also grow rapidly, disseminate widely via the blood stream to the lungs, vagina, liver, kidneys, gastro-intestinal tract and the brain; they are nevertheless almost always amenable to chemotherapy, provided the diagnosis is established before irreversible damage has occurred. The overall survival now stands at 81·5 per cent.

Chorionic gonadotrophin (hCG)

The use of radio-immunoassay (RIA) estimations of chorionic gonadotrophin has undoubtedly made the chief contribution to the curability of these tumours.

Biological assays for detecting hCG were applied in the diagnosis of trophoblastic tumours during the 1930s. The estimation of mouse uterine weight was widely used up to about 1964, but since then, these less accurate methods have been completely superseded by radio-immunoassay of hCG in urine or plasma.

In patients with choriocarcinoma and invasive mole, the amount of hormone produced is roughly proportional to the number of tumour cells present. The average tumour cell has been estimated to produce between 5×10^{-4} and 5×10^{-5} iu hCG/day, so that a patient excreting 10^6 iu hCG/day in the urine has a total body burden of the order of 10^{11} viable tumour cells. When the concentration of hCG is just sufficient to allow for detection of the tumour, it is estimated that there are still between 10^5–10^7 tumour cells present. Routine pregnancy tests generally detect only about 10^8–10^9 tumour cells.

α and β sub-units of hCG

Until recently the limit of detection for small amounts of hCG had been imposed by the cross reaction between hCG and luteinizing hormone (LH). It has now been shown that hCG and the other pituitary polypeptide hormones consist of two non-identical, non-covalently bound sub-units designated α and β. The α sub-units of TSH, LH, FSH and hCG are similar whilst hormone specificity is thought to reside in the β sub-unit. By using an anti-serum raised against the β sub-unit, it is now possible to discriminate between hCG and LH and thus to determine the hCG concentration in urine in the presence of physiological LH levels.

Effect of chemotherapy on hCG excretion

A fall in hCG values follows the start of a course of chemotherapy after some two to six days and may continue for 5–18 days. The rate of fall bears a direct relationship to the sensitivity of the tumour. There is usually a step-wise reduction in hCG values which, when plotted on a log scale, is seen to be consistent with the concept of fractional cell kill.

Treatment is continued so long as hCG can be detected. When gonadotrophin values are in the normal LH range (50–150 iu), it can be concluded that there are still approximately 10^6 tumour cells present. In cases where hCG values have fallen exponentially, some indication of the minimum time required to reach "zero" number of cells can be obtained by extrapolation of the hCG production curve down to the theoretical one-cell level.

Treatment is usually continued well beyond the "extrapolation zero" mark if the tumour had a long latent period before commencement of treatment, if there were large metastases or disease in critical sites such as the brain or liver and in those patients of blood group AB who have a relatively poor prognosis.

Plasma: CSF hCG ratio and detection of intracranial metastases

RIA allows the concentration of hCG to be measured in the CSF; there measurements have proved superior to other methods in the detection of metastases in the central nervous system. A plasma: CSF ratio of hCG of less than 200:1 is strongly suggestive of intracranial disease. When the plasma concentration is falling rapidly, the plasma: CSF ratio may be temporarily disturbed due to the slow rate of diffusion of the hormone into and out of the spinal fluid.

Follow-up after hydatidiform mole

RIA estimation of urinary hCG in a centralized follow-up service now facilitates the process of follow-up after a hydatidiform mole. It allows persistent trophoblastic activity to be accurately assessed, thus identifying those patients who may require chemotherapy for residual disease. With careful collection and interpretation of RIA estimates of urinary hCGm it has been possible to restrict the number of patients receiving chemotherapy to less than 6 per cent.

Alpha-foetoprotein (AFP)

AFP values are usually in the normal non-pregnant range in patients with hydatidiform mole and choriocarcinoma, whereas in a normal pregnancy they are invariably raised after the 12th week of gestation.

Placental alkaline phosphatase

A high level of hCG production together with a low level of placental alkaline phosphatase in the serum provides suggestive but not conclusive evidence for the presence of a mole.

Human placental lactogen (HPL)

The serum concentration of HPL in patients with trophoblastic tumours is well below that of a normal pregnancy of ten weeks duration.

Radiographic studies

(1) A chest X ray should be performed on all these patients. Invasive moles seldom produce more than two metastases. In general pulmonary metastases are an indication for treatment.

(2) Pelvic arteriography plays an important part in the identification of local changes of trophoblastic neoplasia in the uterus and the extent of localized extra-uterine disease, particularly vaginal metastases. It is particularly useful where all visible evidence of disease is lacking yet hCG levels are still raised.

Non-gestational trophoblastic tumours

These highly malignant tumours arise predominantly in the testes in the 18–40 age group. Although trophoblastic elements are often absent from the primary lesion, metastases may consist mainly or exclusively of choriocarcinoma. Earlier diagnosis could be achieved if tests for hCG were more widely used in those age groups presenting with testicular swellings, abdominal masses, back pain, haemoptysis and lung opacities. The poor outlook in the treatment of these tumours is related to the fact that they are usually diagnosed when far-advanced.

REPORT ON TREATMENT OF CANCER OF THE OVARIES

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Rotterdamsch Radio-Therapeutisch Instituut (R.R.T.I.)
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A malignant ovarian tumour has been diagnosed in 373 patients referred to the R.R.T.I. from January 1966 to June 1972. Serous ovarian carcinoma frequently occurred most (254 patients). The results in these patients are studied in detail after staging according to F.I.G.O. recommendations.

Following surgery and post-operative radiotherapy, chemotherapy was started immediately in all patients with progressive disease and, after randomization, also in 50 per cent of the others.

The three-year survival in Stage II patients tended to be more favourable (20–40 per cent) following irradiation of the pelvis and the lumbo-aortic nodes than following radiotherapy restricted to the pelvic area. The dose should be 5–6 krads.

The five-year survival was 68 per cent for Stage I, 26 per cent for Stage II and nearly zero for Stages III and IV, as well as for patients referred for treatment of a recurrence. In spite of whole-abdomen irradiation 50 per cent of the patients of the three groups last-mentioned were deceased within eight months; therefore chemotherapy should be preferred.

The main problem in ovarian cancer is the late diagnosis. Evaluation of results is difficult because numerous variable factors concerning pathology and treatment force to subdivide in groups too small for statistically reliable conclusions. Each treatment factor should be studied by a group of hospitals.

ADVANCES IN THE TREATMENT OF MALIGNANT DISEASE IN CHILDREN

Dorothy Pearson

Christie Hospital and Holt Radium Institute,
Withington, Manchester M20 9BX

The management of children with malignant disease has changed, principally by the introduction of chemotherapy used prophylactically to try to improve survival.

Four tumour groups are used to show the improvement in survival which has occurred.

The addition of B.C.N.U. and Vincristine in the management of medulloblastoma, ependymoma, and malignant astrocytoma gives encouraging preliminary results in that of 11 patients at a year or more from diagnosis, only one has died and he of a brain haemorrhage. In the same time interval in the past at least 54 per cent would have died.

The embryonic sarcomas of soft tissue also show improvement since the introduction of chemotherapy, particularly multiple drugs, so that in certain sites, such as the bladder, patients have survived whom previously would have died.

It is recognized that the addition of Actinomycin D in the management of children with Wilm's tumour gave better results, raising a 29 per cent survival to 59 per cent. Recent trials have shown an improvement in this when using a very intensive course of Vincristine or when combining Actinomycin D and Vincristine. Another important feature in Manchester was the centralization of surgery, which changed the survival from 30 to 60 per cent.

Finally, Ewing's tumour of bone has shown improved survival by adding Vincristine and Cyclophosphamide to the management. There being a difference in survival at three years. Before chemotherapy the survival was 15 per cent and with chemotherapy is 68 per cent.

1976, *British Journal of Radiology*, *49*, 294

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

EVALUATION OF A NEW SCREEN/FILM COMBINATION

Evans *et al.* (1975) have investigated the Trimax system of rare-earth screens and green-sensitive films by measuring relative sensitivities, γ values and "contrast transfer functions". Their main conclusion is that "The Trimax system offers the possibility of reducing exposures for the majority of diagnostic X-ray examinations by factors of about 4 *without a reduction in the quality of the image*" (my italics).

However, the quality of the radiographic image depends, in addition to the factors mentioned above, on its displayed noise. This noise is not measured by any determination of contrast transfer function (Hay, 1969). Therefore, although their main conclusion might perhaps be true, I consider that it is not supported by their measurements, and I believe the statement to be potentially misleading to clinical users.

Radiographic noise is compounded of X-ray quantum noise, screen structure noise and film emulsion noise. Reducing the X-ray dose by a factor of 4 increases the relative quantum noise inherent in the X-ray beam incident on the cassette by a factor of 2. Though this deterioration might be reduced by greater fractional absorption in the new screens, the situation is complex (Stevels, 1975), and the properties of the new materials might well result in an increase in the levels of screen structure noise and of film emulsion noise.

Predictions of image quality based solely on objective measurements are inevitably uncertain, but until adequate measurements of noise are made on the new system (a difficult task), the conclusion of Evans *et al.* (1975) will be even more uncertain.

Yours, etc.,
G. A. HAY.

Department of Medical Physics,
University of Leeds,
Leeds LS1 3EX.

REFERENCES

EVANS, A. L., DAVISON, M., MCLELLAN, J., and JAMES, W. B., 1975. Evaluation of a new screen/film combination. *British Journal of Radiology*, *48*, 858–859.

HAY, G. A., 1969. Objective measurements of noise in X-ray television systems. In *Television in Diagnostic Radiology*, eds. R. D. Moseley and J. H. Rust (Birmingham, USA).

STEVELS, A. L. N., 1975. New phosphors for X-ray screens. *Medicamundi*, *20*, 12–22.

THE EDITOR—SIR,

AN INVESTIGATION OF THE PHARMACOLOGICAL AND RADIOSENSITIZING EFFECTS OF THE 2-NITROIMIDAZOLE RO–07–0582 IN PRIMATES

A study using primates is in progress at Roswell Park Memorial Institute, Buffalo, New York, in conjunction with Dr. G. Adams of the Gray Laboratory, Middlesex, England, to determine the maximum radiosensitizing effect of Roche–07–0582 [1–(2–nitro–1–imidazoyl)–3–methoxy–2–propanol] that can be obtained with an acceptable drug dose level in order to determine the feasibility of a phase I clinical study (Asquith *et al.*, 1974). It is considered that for a single dose an enhancement ratio of 1·5 for hypoxic skin is necessary for a successful phase I clinical study.

Stumptail monkeys weighing 10–15 kg, maintained in our Springville primate colony, were used for the experiment. In view of the known variation of absorption of this drug when given by mouth, intravenous administration was used. Blood serum concentrations were measured by a polarographic technique (DeSilva, Munno and Strojny, 1970). For toxicological studies autopsies were performed and, in view of the reported damage to Purkinje cells in dogs (Scharer, 1972), the brains were submitted to a neuropathologist for histological examination.

In preliminary toxicological studies, a drug dose of 800 mg/kg caused intermittent convulsions and death of the animal within three days after administration of the drug. The autopsy showed no abnormal findings. Brain histology is not yet available.

Enhancement by the radiosensitizer was investigated using a special clamp which provided hypoxic areas of skin for irradiation with a range of doses from 3,000–5,000 rads using 6 MeV X rays. Hypoxia was ensured by clamping the skin 15 minutes prior to irradiation. Skin flaps from the lumbar region of the back were used in all experiments and these areas were shaved before irradiation. On one side of the monkey, three clamped test areas and an unclamped area were irradiated before injection of the drug and identical areas were irradiated on the other side one hour after an intravenous dose of 07–0582. Ratios of enhancement were calculated by comparing (visually) the response of the skin to the radiation on the two sides of the monkey. To simulate a possible clinical programme, enhancement ratios were obtained at the beginning and at the end of a course of 07–0582 given twice weekly over a three-week period. The results shown in Table I indicate that the one-hour blood serum concentration of the drug is directly related to the dose of drug administered when it had not been previously administered to the animal. If the drug was administered twice weekly for a three-week period, one-hour serum levels at the end of the three-week period were found to be one-quarter of the value obtained for the initial dose of the drug, suggesting that the drug is possibly causing enzyme induction which may degrade subsequent doses of the drug. Animals 3 and 4 also exhibited evidence of possible enzyme induction following weekly dosages of 07–0582.

Enhancement ratios for clamped skin correlated well with the serum concentration of the drug and exhibited values of 1·3 for 100 mg/kg and 1·6 for 200 mg/kg of the administered drug. Animal 5, which was given twice weekly injections of 100 mg/kg, resulting in low serum levels for the last drug injection, showed an enhancement of only 1·1 for the last administration of the drug. No effect of the sensitizer on well-oxygenated skin was observed in these experiments. These preliminary results suggest that enhancement ratios of 1·5 may be obtained with serum drug levels of 200 μg/ml, which future toxicological studies may show to be acceptable (clinically).

Enzyme induction may, however, decrease the effectiveness of the drug which would exclude frequently repeated doses of the drug unless the drug dosage can be increased without causing increased toxicity. It is possible, however, that a single dose of the drug may be insufficient to cause persistent enzyme induction, in which case the sensitizer might be used in conjunction with the first and last doses of a course of radiation.

Yours, etc.,
R. JOHNSON,
C. GOMER,
J. AMBRUS,
J. PEARCE,
D. BOYLE.

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TABLE I

ENHANCEMENT RATIOS OF Ro–07–0582

Monkey number	Previously administered Ro–07–0582 (mg/kg)	Drug dose on day of irradiation (mg/kg)	Drug serum level (1 h after injection) (μg/ml.)	Enhancement
1	none	100	160	1·3
2	none	200	310	1·6
3	50 (Day 0)		75	
	100 (Day 7)		110	
		200 (Day 14)	140	1·4
4	50 (Day 0)		110	
	100 (Day 7)		110	
	200 (Day 14)		230	
		400 (Day 21)	310	1·7
5		100 (Day 0)	160	1·3
	100 (Day 3)			
	100 (Day 7)			
	100 (Day 10)			
	100 (Day 14)		70	
	100 (Day 17)			
	100 (Day 21)			
		100 (Day 24)	40	1·1

ACKNOWLEDGMENT

This work was performed in co-operation with the Gray Research Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England and Roche Inc., Nutley, New Jersey 07110.

REFERENCES

ASQUITH, J. C., WATTS, M. E., PATEL, K., SMITHEN, C. E., and ADAMS, G. E., 1974. Electron affinic sensitization. V. Radiosensitization of hypoxic bacteria and mammalian cells *in vitro* by some nitroimidasoles and nitropyrazoles. *Radiation Research*, *60*, 108–118.

DESILVA, J. A. F., MUNNO, N. and STROJNY, N., 1970. Absorptiometric, polarographic, and gas chromatographic assays for the determination of N–1–substituted nitroimidazoles in blood and urine. *Journal of Pharmaceutical Sciences*, *59*, 201–210.

SCHARER, K., 1972. Selective injury to Purkinje cells in the dog after oral administration of high doses of nitroimidazole derivatives. *Verhandlungen der Deutchen Gesellschaft für Pathologie*, *56*, 407–410.

THE EDITOR—SIR,

THE LYMPHOCYTE RESPONSE TO PHYTOHAEMAGGLUTININ AFTER "IN VITRO" IRRADIATION

Song and Levitt (1975) have commented that Braeman and Moore (1974) showed a greater degree of suppression by radiation of the phytohaemagglutinin (PHA) stimulation of human lymphocytes than is found by other authors. Thus, they had found no effect from a dose of 1,000 rads to rat lymphocytes, whereas Braeman and Moore had reported a transformation index reduced to 25 per cent of normal after 800 rads to human lymphocytes when using a morphological index of transformation.

Among the authors quoted by Song and Levitt (1975) were Ilbery *et al.* (1971) whose transformation index is based upon scintillation counting of the uptake of ^{3}H-thymidine by lymphocytes from buffy coat preparations of human blood cultured for 72 hours after PHA stimulation after irradiation.

We have used a modification of their technique (including a ficoll-hypaque gradient procedure which separates more than 90 per cent lymphocytes from human blood) and we find an exponential dose-response curve for ^{60}Co γ irradiation. After 1,000 rads the transformation index is reduced to 37 per cent, comparable to the value of 28 per cent found by Ilbery *et al.* (1971) for that dose.

Braeman and Moore (1974) use a different technique, of course, but these three sets of data with human lymphocytes show a significant radiation response which is quite different from the observations quoted by Song and Levitt (1975) with rat lymphocytes.

Yours, etc.,

H. M. A. YOSEF,

A. H. W. NIAS.

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Glasgow G31 4PG

REFERENCES

BRAEMAN, J., and MOORE, J. L., 1974. The lymphocyte response to phytohaemagglutinin after *in vitro* irradiation. *British Journal of Radiology*, *47*, 297.

ILBERY, P. L. T., RICKINSON, A. B., and THRUM, C. E., 1971. Blood lymphocyte replicating ability as a measurement of radiation dosage. *British Journal of Radiology*, *44*, 834–840.

SONG, C. W., and LEVITT, S. H., 1975. The lymphocyte response to phytohaemagglutinin after *in vitro* radiation. *British Journal of Radiology*, *48*, 504.

1976, *British Journal of Radiology*, *49*, 296

Correspondence

THE EDITOR—SIR,

WHICH? ON RADIATION

Dr. Saxton's comments on the necessity for continual education of clinicians and indeed of staff in X-ray departments is timely. In an investigation we carried out in this department (McCreath *et al.*, 1975) we found that 4·5 per cent of all females of childbearing age and 2·4 per cent of those referred for examinations including the pelvis appeared to be at risk of pregnancy at the time of request. We agree that the problem cannot be solved by "crisp, once for all action" but requires continuous vigilance. Your readers may therefore be interested in one part of our attempted solution to this problem of continuing education. In addition to including a "ten-day rule" section on the front of the request card we include on the reverse of the request card abbreviated reminders of the clinically important sections of the Code of Practice and in particular remind the clinician of his responsibility for observing the "ten-day rule" (Fig. 1). We cannot claim this to be infallible but at least no clinician can say that he was unaware of the procedure or had forgotten the details.

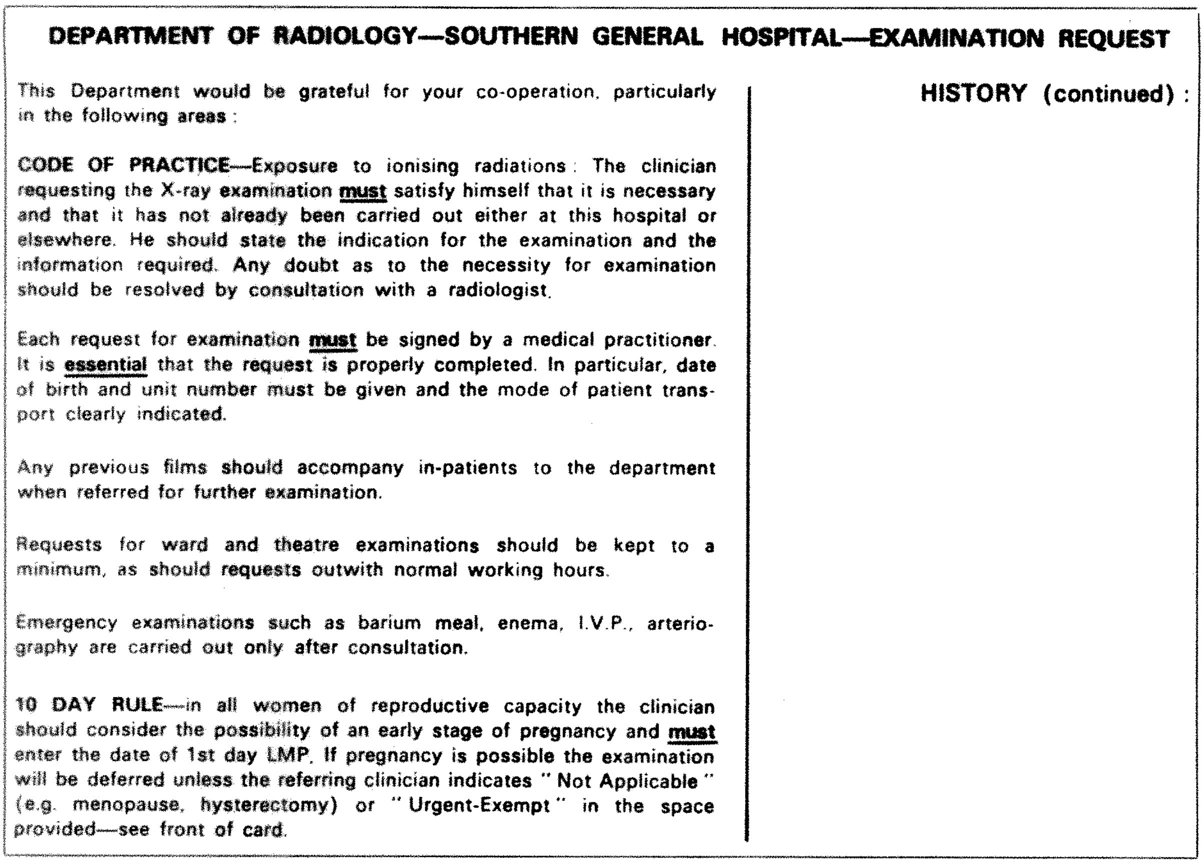
Yours, etc.,

W. B. JAMES,
G. MCCREATH.

Department of Radiology,
Southern General Hospital,
Glasgow, S.W.1.

REFERENCE

MCCREATH G., BALLINGER, M., and JAMES, W. B., 1975. The Ten-Day Rule. *Health Bulletin* (*Scottish Home and Health Department*), *33*, 14–17.



DEPARTMENT OF RADIOLOGY—SOUTHERN GENERAL HOSPITAL—EXAMINATION REQUEST

This Department would be grateful for your co-operation, particularly in the following areas :

CODE OF PRACTICE—Exposure to ionising radiations : The clinician requesting the X-ray examination **must** satisfy himself that it is necessary and that it has not already been carried out either at this hospital or elsewhere. He should state the indication for the examination and the information required. Any doubt as to the necessity for examination should be resolved by consultation with a radiologist.

Each request for examination **must** be signed by a medical practitioner. It is **essential** that the request is properly completed. In particular, date of birth and unit number must be given and the mode of patient transport clearly indicated.

Any previous films should accompany in-patients to the department when referred for further examination.

Requests for ward and theatre examinations should be kept to a minimum, as should requests outwith normal working hours.

Emergency examinations such as barium meal, enema, I.V.P., arteriography are carried out only after consultation.

10 DAY RULE—in all women of reproductive capacity the clinician should consider the possibility of an early stage of pregnancy and **must** enter the date of 1st day LMP. If pregnancy is possible the examination will be deferred unless the referring clinician indicates " Not Applicable " (e.g. menopause, hysterectomy) or " Urgent-Exempt " in the space provided—see front of card.

HISTORY (continued) :

FIG. 1.

1976, *British Journal of Radiology*, *49*, 297

Correspondence

THE EDITOR—SIR,

MATHEMATICAL REPRESENTATION OF MEGAVOLTAGE TELETHERAPY BEAMS

The publication in the September issue of this journal of three consecutive papers (Wilkinson and Redmond, 1975; Kornelson and Young, 1975; Thomas and Haybittle, 1975) using empirical formulae to represent megavoltage teletherapy beams prompts us to raise some criticisms of this method and to suggest an alternative which differs both from empirical formulae and from methods requiring the storage of large quantities of data on the dose distribution in many beams (for example Milan and Bentley, 1974).

In the method of empirical formulae, mathematical functions are proposed which model megavoltage beams in such a way that the number of adjustable parameters is minimized. The values of most of the parameters appropriate to a given treatment machine must be determined by comparison of the model with dose measurements at special points in the beam. A set of values is chosen for the parameters as a first approximation and the doses at the special points are calculated using the empirical formulae. The calculated doses are compared with the measured doses and the values of the parameters are adjusted. The process is repeated to find better approximations to the best set of values of the parameters.

This method of representing megavoltage beams leads to limitations:

(1) Because the formulae are chosen empirically rather than on strictly physical grounds, the range of validity is indeterminate. It is always uncertain whether formulae used for one machine will give an acceptable fit to the measured doses over the whole operating range of a similar but different machine. Extensive checking is therefore required, which calls for more data on dose distribution in the beam than would appear necessary at first glance.

(2) Functions which are chosen so as to minimize the number of adjustable parameters lead to expressions which cannot be evaluated quickly in a computer program. For example exponentials and non-integral exponents take longer to evaluate than the interpolations used in the beam data storage methods.

(3) The parameters are of no interest in themselves. Their determination is an unnecessary stage between the measurement of dose at selected points and the computation of dose at other points in the beam. The empirical formulae impose on the calculated doses a certain form which may or may not correspond with reality. The relationship between measured and calculated doses is thus less direct.

These limitations can be avoided by using a system of representation based on known approximations to the radiation physics of megavoltage beams, which derives calculated doses by minimal computation from a small set of dose measurements which completely characterize a treatment machine.

Such a system has been developed at Sheffield from previous work in this field (Day, 1950; Jayaraman, 1970) as an alternative to beam data storage and empirical formulae. The radiation physics is rigorous apart from easily verified approximations. On this system, the measurements which competely characterize a treatment machine are:

(1) dose versus depth and field size (typically 80 points);
(2) penumbra profile (20 points);
(3) profiles of any wedges used (20 points/wedge).

The method uses the measured data to calculate the dose distribution directly. The calculation can be rapidly executed by computer using little more than linear interpolation. A program has been written which successfully tests the method and another program suitable for routine planning has been written around a Computer Display Terminal with Graphics Tablet. Both programs are in FORTRAN.

Yours, etc.,
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C. K. BOMFORD.

Medical Physics Department,
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REFERENCES

DAY, M. J., 1950. A note on the calculation of dose in X-ray fields. *British Journal of Radiology*, *23*, 368–369.

JAYARAMAN, S., 1970. A computer method for calculating multi-field and rotational dose distributions in Co-60 teletherapy. *Strahlentherapie*, *140/3*, 283–285.

KORNELSON, R. O., and YOUNG, M. E. J., 1975. Empirical equations for the representation of depth dose data for computerised treatment planning. *British Journal of Radiology*, *48*, 739–748.

MILAN, J., and BENTLEY, R. E., 1974. The storage and manipulation of radiation dose data in a small digital computer. *British Journal of Radiology*, *47*, 115–121.

THOMAS, R. L., and HAYBITTLE, J. L., 1975. A widely applicable method for computing dose distribution from external megavoltage beams. *British Journal of Radiology*, *48*, 749–754.

WILKINSON, J. M., and REDMOND, W. J., 1975. Experience in implementing the Mark III rad 8 system for radiotherapy dose computations. *British Journal of Radiology*, *48*, 732–738.

THE EDITOR—SIR,

TECHNETIUM BONE-SCANNING COMPLEXES

The recent review of bone-scanning reagents by Merrick (1975) raises a number of points with regard to technetium polyphosphate complexes which are open to discussion. Whilst it is reported that phosphates labelled with ^{32}P or chelated with ^{51}Cr localize in bone, the fact that ^{51}Cr phosphate chelates accumulate in bone to a greater extent than non-chelated phosphates is overlooked (Anghileri and Miller, 1971). This phenomenon suggests that the presence of Chromium enhances the bone-seeking capacity of such compounds, a fact which is not surprising since most heavy metals accumulate in the skeleton.

Work in our laboratories (Cox, 1974) has clearly demonstrated that technetium complexed with stannous chloride or titanium chloride localizes in bone in the absence of chelating agents, phosphate or otherwise. It is therefore most likely that in all of these technetium compounds, bone localization is due to an inherent bone-seeking capacity of the technetium tin complex, which is probably related to the bone localization of heavy metals.

Our experiments suggest that the function of the various polyphosphates lies in the prevention of particulate colloid (technetium tin oxide) formation, which is reflected in the degree of RES uptake, hence the observed liver, spleen and marrow activity, probably by preventing oxidation beyond the technetium (v) state. Technetium (v) complexes are readily excreted in the urine (Yeh and Kriss, 1967), which could account for the low tissue background observed with pyrophosphate, diphosphonates and hexametaphosphate, all compounds with a strong chelating effect. In support of this, we have observed that if one passes technetium polyphosphate (Diagnostic Isotopes Inc.) reagent, which normally has a high RES component, over a 10 nM filter immediately prior to injection, the RES uptake is almost completely eliminated and similar uptake patterns are obtained to those of pyrophosphate and diphosphonate.

It is our opinion that the choice of reagent should be related to the type of lesion. When seeking malignancy, it should be borne in mind that the majority of skeletal metastases originate in the bone marrow. In patients with known primary malignancy, negative X rays, but skeletal localized pain, we have obtained a diagnostic accuracy for metastases in excess of 90 per cent by using a polyphosphate complex with a significant bone marrow uptake (Polyphosphate-Diagnostic Isotopes Inc.). Many of these lesions are visualized six months and more before they are detectable by other means.

Similarly by using a bone specific reagent (Pyrophosphate BYK-Mallinckrodt) it has been possible to quantitatively evaluate the rate of ectopic bone formation following trauma. Clearly there are many things still to be learned regarding the nature of these various complexes and their application to clinical situations, but it is our belief that the view stated above best fits the known facts and that on this basis optimal interpretation of clinical situations can be made.

Yours, etc.,
P. H. Cox.

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REFERENCES

Anghileri, L. J., and Miller, E. S., 1971. ^{51}Cr polyphosphates, their general behaviour in normal and tumour bearing animals. *Journal of Nuclear and Biological Medicine*, *15*, 42–49.

Cox, P. H., 1974. ^{99}Tc^{m} complexes for skeletal scintigraphy. Physico-chemical factors affecting bone and bone uptake. *British Journal of Radiology*, *47*, 845–850.

Merrick, M. V., 1975. Review article: bone scanning. *British Journal of Radiology*, *48*, 327–351.

Yeh, S. H., and Kriss, J. P., 1967. Distribution and scintiphotography of a new complex pentavalent technetium ^{99m} citrate: studies in the rodent. *Journal of Nuclear Medicine*, *8*, 666–677.

The Editor—Sir,

Dosimetry of the Fast Neutron Beam Produced by the MRC Cyclotron

The fast neutron beam produced by the Medical Research Council's cyclotron at Hammersmith Hospital, London, has been in use for radiotherapy since 1966 and for radiobiology for several years previous to that date. Since the inception of the fast neutron beam at Hammersmith we have been concerned particularly with maintaining reproducible and internally consistent dosimetry, with the knowledge that the absolute accuracy with which the accepted unit of absorbed dose, the rad, could be realized was poor. However, the increasing use of fast neutrons for radiotherapy demands that all centres should have a common basis for neutron dosimetry. Since no standardizing laboratory currently offers a calibration service for fast neutron beams, further efforts have been devoted to improving the accuracy of fast neutron dosimetry both at Hammersmith (*e.g.* Bewley *et al.*, 1974) and elsewhere, while physicists from Glasgow, Manchester, Houston and Washington, D.C., have visited Hammersmith to carry out intercomparisons. These measurements have indicated that the 'Hammersmith' rad of neutrons represented 108 ergs/g. Consequently, from January 1, 1975, fast neutron dosimetry at Hammersmith was revised by 8 per cent to obtain better consistency between the various centres. The dose prescribed for radiotherapy is now typically 1,560 rads given in 12 treatments in 26 days instead of 1,440 rads as prescribed previously. It must, however, be emphasized that this does not result in an increase in the amount of radiation received by the patient. Also, all values of RBE cited heretofore should be reduced by 8 per cent to bring them into accord with current dosimetry.

Confusion can sometimes arise because some centres quote only the dose due to neutrons and ignore the dose due to the accompanying γ radiation (*e.g.* Hammersmith) while other centres quote the total dose obtained by a simple addition of the dose due to the two components. For the irradiation of biological materials neither approach is strictly correct, the effective dose probably lying between these two extremes, owing to the different biological properties of the two types of radiation. The best procedure is to record separately both components of the total dose.

Yours, etc.,
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D. K. Bewley.

MRC Cyclotron Unit,
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Ducane Road,
London W12 0HS.

REFERENCE

Bewley, D. K., McCullough, E. C., Page, B. C., and Sakata, S., 1974. Neutron dosimetry with a calorimeter, *Physics in Medicine and Biology*, *19*, 831–842.

The Editor—Sir,

The "Self-Reporting Radiograph"

With reference to the letter from Rubem Pochaczevsky in The British Journal of Radiology, *48*, 65, I suggest the writer and others requiring quick, easily made small prints of radiographs try using a Polaroid camera. For many years I have been producing in a few minutes prints of quality good enough for reproduction in medical journals using a vintage Polaroid equipped with a close-up lens kit. The ideal set-up is to have the camera mounted on a rail adjustable for distance and always centred on the middle of the film illuminator, and mark the rail to show area of coverage and camera focal settings. However the tape provided with the lens kit and a pile of Journals is a workable substitute. These old cameras can be picked up cheaply from photographic stores and, if the results should not be satisfactory, they will be welcomed by the children. I find the makers recommended 10-second processing time is better lengthened to 45 seconds. Perhaps this is something to do with being in the southern hemisphere.

Yours, etc.,
G. L. Hardman.

26 Spring Gully Road,
Bendigo, Victoria 3550,
Australia.

The Editor—Sir,

Should we Report Every Film?

You ask in your editoral whether the radiologist must report every film. It would be more pertinent to ask whether he is physically capable of reporting every film. The present shortage of radiologists is likely to continue because of diminishing recruitment, emigration, increasing quantitative demands, widening horizons and expanding administrative duties. A desirable standard of radiology cannot be maintained with a workload in excess of 5–12,000 examinations per year, depending on the type of practice concerned. Most radiologists' workload is at least half as high again.

What is to be done? The importance of efficient departmental organization is obvious. It is tempting to delegate or ignore administrative work, but this is a shortsighted policy. Departmental administration must remain firmly in the hands of radiologists. We are not likely to reduce the total number of examinations performed, though the annual increase reported by many departments should not be accepted at face value. With a free service, demand will always rise to absorb all the resources available. It is part of the purview of the radiologist to monitor and to resist unwarranted increases in demand.

The only practical approach is to ration film reporting. Three groups of radiological examinations can be identified.

(1) Routine examinations for consultants who are competent to interpret them without the assistance of the consultant radiologist.
(2) Routine examinations for non-specialists, such as general practitioners or casualty officers.
(3) Special examinations, including contrast examinations and other procedures specifically undertaken or controlled by the radiologist.

It would be in the interests of the patient if the radiologist's limited time was not spent in the routine reporting of group (1) examinations such as those originating in hospital out-patient clinics and from in-patients being investigated and treated in hospitals in which there is a full-time consultant radiologist cover. Examinations initiated through the open service must be reported. Some relief from casualty reporting is possible if only those cases interpreted by the casualty officers as normal are subsequently referred back for a report. Such an approach could release the consultant radiologist from up to 40 per cent of his reporting duties. This time might be used to increase the number of special examinations undertaken, or increase his availability for consultations in the radiology department and on the ward. These consultations would result in a recorded opinion on examinations already performed.

There are many advantages: a greater throughput in departments whose workload is now restricted by the capacity of the radiologist to report, more time for consultations with clinicians about patients with particular problems, and more effective use of radiological resources as the result of consultation before examinations are initiated. This scheme would have no place in departments training radiologists. There are two particular disadvantages. Routine films sent to specialists or their junior staff might be misinterpreted, to the detriment of the patient. Against this must be weighed the cases presently interpreted incorrectly by the radiologist as a direct result of the reporting workload. The other problem is that of quality control. There may be a diminution in the quality of examinations which are not routinely seen by the radiologist. This should be prevented by placing an increased responsibility for quality control on senior radiographers. The concept of allowing some examinations to go through the department without a report is not radical. It already happens in some departments, either by choice or by necessity. There should be no concern at the legal implication. The crucial question is "What is the most responsible way to manage the limited resource of radiological facilities?"

In summary, you have highlighted the main problem resulting from a shortage of diagnostic radiologists. The only logical solution to the short-term problem is to stop reporting routine radiological examinations performed at the request of a clinician competent to interpret the examination for himself. Such a re-organization of the radiologist's work pattern would allow for an increase in the volume of special examinations that he undertakes, and would increase his availability for consultations on the ward and in the department.

Yours, etc.,
MICHAEL J. BRINDLE.

Department of Radiology,
West Norfolk and King's Lynn General Hospital,
London Road, Kings Lynn, Norfolk PE30 5QD.

1976, *British Journal of Radiology*, *49*, 300–301

Forthcoming events and other notices

The editors have decided that owing to the extreme shortage of space in the *British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and meetings announcements specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meetings announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

British Nuclear Medicine Society Annual Meeting

With the Hospital Physicists Association, is to be held on March 25–26, 1976, at the University of London Students Union, Malet Street, London, W.C.1.

Further information from Dr. D. N. Croft, Department of Nuclear Medicine, St. Thomas' Hospital, London SE1 7EH.

Annual Congress and Scientific Exhibition

To be held on April 8–9, 1976 at the University College, London. For information and registration please contact the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiology of Visceral Venous Obstruction

The Mackenzie Davidson Memorial Lecture, by Dr. M. Viamonte, Director of Radiology, University of Miami, School of Medicine, to be given at the University College, London, April 8, 1976.

Institute of Acoustics Spring Conference 1976

To be held at Engineering and Science Building, Liverpool Polytechnic, Byrom Street, Liverpool 3, April 12–14, 1976.

Contributions are invited and should be submitted to Dr. R. Lawrence, Principal Lecturer, Acoustics Group, Physics Department, Liverpool Polytechnic.

Further information and registration from The Secretary, Institute of Acoustics, 47 Belgrave Square, London SW1X 8QX.

Medical Images: Formation, Perception and Measurement

The Seventh L. H. Gray Conference, which will be concerned with the fundamentals of medical images, will be held at the University of Leeds, England, on April 13–15, 1976.

Address for further information: Dr. M. J. Day, Regional Medical Physics Department, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, England.

The following meeting is to be held at the British Institute of Radiology, Institute House, 32 Welbeck Street, London W1M 7PG.

The Use of Hyperthermia and Non-Ionizing Radiation in the Treatment of Cancer, May 21, 1976

Further information from the General Secretary; address as above.

Postgraduate Course in Tomography of the Temporal Bone

To be held in Copenhagen, June 3–4, 1976. The course is sponsored by the I.C.R., the A.E.R. and the Scandinavian Association of Radiologists, and will be directed by Dr. Sam Brünner, president of the Congress.

For further information and registration, please contact Dr. Paul E. Andersen, Department of Radiology, University Hospital, 5000 Odense, Denmark.

Health Physics Summer School

The 17th annual Summer School in Health Physics (Radiation Protection) will be held at Imperial College from June 21, to July 2, 1976.

Initial enquiries should be sent to Dr. H. D. Evans, Department of Chemical Engineering, Imperial College, London SW7 2AZ.

Breast: Non-Cancerous Diseases

To be held in Strasbourg, France, June 30–July 3, 1976. The 4th International symposium on Senology, under the auspices of the European Association of Radiology; includes study-groups with invited lectures and methods, mastopathies and lactation; proffered papers on topics covered by the above three study-groups and additionally; infections, malformations, breast pathology, computer analysis, comparative psychology and breast functions; a scientific exhibition and a technical exhibition.

The symposium will be preceded by postgraduate teach-ins, on June 28, 29, ultrasonography (by Société Française d'Echographie) on June 29, thermology (European Thermographic Association) and on June 29, xerography.

Apart from the postgraduate teach-ins, there will be simultaneous translation in the official languages of the symposium – English, French and German.

Further information from Symposium Sénologie 1976, Professor Charles Gros, Palais des Congrès, 67000 Strasbourg, France.

Computers in Radiotherapy in Europe

It is proposed to hold a Workshop at IAEA, Vienna, on July 5–10, 1976, organized by the Groupe Informatique, A.E.R. with the support of the European Association of Radiology. The aim will be to establish the contribution that the computer makes at the clinical level in the fields of dose computation, clinical records, radiobiology, etc., and to determine future development.

Further information from Dr. D. N. Edwards, Clinical Research Unit, Mersey Regional Centre for Radiotherapy and Oncology, Clatterbridge Hospital, Bebington, Wirral, Merseyside L63 4JY, U.K.; or Dr. T. Moller, Radioterapikliniken, Lasarettet, S-221 85 Lund, Sweden.

First Meeting of the World Federation of Ultrasound in Medicine and Biology

This meeting, to be held August 3–7, 1976 in San Francisco is the third world congress on ultrasonics in medicine.

Reduced registration fees are payable by members of the international sub-group of the British Medical Ultrasonics Group.

Further information from: 1st W.F.U.M.B., PO Box 25606, Oklahoma City, Oklahoma 73125, U.S.A.

For information above B.M.U.G. contact the General Secretary, B.I.R., 32 Welbeck Street, London W1M 7PG.

Forthcoming events and other notices

8TH CONGRESS OF THE SOCIETY OF HUNGARIAN RADIOLOGISTS AND 12TH ANNUAL MEETING OF THE EUROPEAN SOCIETY FOR RADIATION BIOLOGY

To be held in Budapest, Hungary, October 19–22, 1976.

For further information please contact the Congress Office (H-1361 Budapest, PO Box 32, Hungary).

RADIATION PROTECTION: AN EXAMPLE OF ACTION AGAINST MODERN HAZARDS

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P. no. 33, 92260 Fontenay-aux-Roses, France.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colégio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Book reviews

Efficiency and Limits of Radiologic Examination of the Pancreas. Edited by Herman Anacker, pp. 276, 1975 (Stuttgart, Georg Thieme), DM68.

A most successfully edited collection of papers read at the Symposium Radiologicum Pancreatis held in Munich in 1973. Obviously not all the 46 papers are of great merit. Among the most valuable are the radiological anatomy of the pancreas by Professor Anacker, a contribution on the value and limitations of the examinations of the gastro-intestinal tract in pancreatic disease by Professor Swart, hypotonic duodenography in the diagnosis of pancreatic disease by Professor Gerhardt and papers on pancreatic angiography by Dr. Tylen, by Dr. Reuter and by Drs. Rösch and Holman.

Retrograde pancreatography is well dealt with in several papers grouped together with Dr. Kreel's most relevant account of the variations of the pancreatic duct normally found in old age.

Three separate résumés present important conclusions, and indicate the most suitable technique or combination of techniques for use in an individual case of pancreatic disease.

This is a most valuable up-to-date account of all that can radiologically be done in the diagnosis of pancreatic disease and is a "must" for every major clinical and radiological department.

H. HERLINGER.

Fibre-Optic Endoscopy. By P. R. Salmon, pp. 237, 1974 (Pitmans Medical Publishing Co. Ltd.), £4·50.

This modestly priced paperback is not a treatise on endoscopic pathology, and does not set out to discuss the place of gastro-intestinal endoscopy in the management of disease. It is described in its preface as an authoritative account of the paraphernalia surrounding endoscopy. It is essentially a practical manual, from which the apprentice endoscopist, nurse or technician may glean in a few evenings what it would otherwise take them many months to absorb. Endoscopic equipment is described in minute detail with sections on the organization of an endoscopy service, the techniques of endoscopy procedures, endoscopic photography and the handling of biopsy and cytology specimens. The didactic approach is generally successful, but leads to some dogmatic statements where there is room for more than one opinion, as for example the advice that a side viewing gastroscope should be passed blind until resistance is felt, when it will usually lie in the antrum. Many endoscopists would prefer to orientate themselves at the cardia and advance through the stomach under direct vision. Parts of the book on instrument detail will become out of date fairly quickly, and stricter editing could avoid repetition, mainly in the chapters on procedures and on radiology. The latter is titled "The role of radiology in fibre-optic endoscopy" and this accurately describes the approach. There are sections on radiology before and during endoscopy, on associated procedures and on radiation protection, and there is a brief tabulation of some radiological indications for endoscopy. The most helpful part is a very clear detailed account of radiological technique in pancreatic and bile duct cannulation. There is no comparison of the accuracy of endoscopy and radiology and no discussion of the clinical role of these two disciplines in the management of disease. The problem of how radiology and endoscopy should best be linked, the possible role of the radiologist endoscopist, the extent to which physicians and surgeons should be encouraged or permitted to use radiological facilities unsupervised are all topics which would be of interest to radiologists. Despite these limitations, the book must be judged on its stated aim of being a practical technical guide. As such it has certainly succeeded, containing a vast amount of information, clearly and simply laid out and it is easy to read. Every endoscopy department should have a copy and it can be thoroughly recommended to all would-be endoscopists.

G. W. STEVENSON.

1976, *British Journal of Radiology*, *49*, 302

Book review

An Introduction to Radiologic Science. By Robert M. Oman, pp. 189, 1975 (Berkshire, McGraw Hill Book Co. (UK) Limited), £5·35.

In the preface to this very small book, the author states that it is intended as a "text for those studying radiologic science for the first time and as a general reference for experienced technologists". It is totally inadequate for both groups; indeed, it is impossible to imagine what kind of reader could benefit from it. The treatment is extremely superficial, and at a very low level.

The first four chapters (entitled: "Elementary principles and mechanics", "Structure of Matter", "Electricity" and "Magnetism and Electromagnetism") attempt to deal—in 86 small pages—with the basic science of the subject. All of the relevant material presented—and very much more—would be well known to any student seeking to register with The (British) Society of Radiographers. At the end of each chapter there are several problems relevant to the subject of the chapter. These problems range from the insultingly simple (*e.g.* "Express your own height in meters and your mass in kilograms") through the irrelevant (*e.g.* "Draw the Helium atom to scale") to the impossible (*e.g.* "Calculate the ratio space taken up by the atoms to the total space in a simple cubic structure").

Chapters 5 to 8 (entitled "X-ray Circuitry", "X-rays", "X-ray Equipment" and "Radiation") deal—in a further 85 small pages—with the "specifically X-ray topics". Again the treatment is inevitably superficial, but in addition, especially in respect of the more applied aspects of the subject there are too many misleading, ambiguous and even some potentially dangerous statements. To detail all is inappropriate and the following examples must suffice:

(1) The diagram showing the characteristic X-ray spectrum is of a single smooth curve extending over a range of wavelengths nearly one-half as great as that used on a previous diagram for the continuous X-ray spectrum. In both cases—as with all the graphs in this book—there are no numerical values or other indication of scale on the axes. A third diagram of the combined spectra, which otherwise might have helped remove this inconsistency, is ruined by an unfortunate printing error (incidentally, the only error of typescript detected).

(2) In the 12-line description of the construction, effect of exposure on, and the processing of an X-ray film, it is stated that "after development, the silver halide crystals not irradiated [*sic.*] are desensitized or 'fixed' so that exposure to light does not result in the formation of silver specks". That this is not true is valuably demonstrated by the large quantity of silver recoverable from the "fixing" solution into which it has been *dissolved.* This kind of error, of which there are several, seems to indicate an undesirable lack of contact with the practice of radiology.

(3) Film speed is "defined as the amount of exposure measured in R/cm.^{2} required to produce a density of 1·0". Not only is this wrong in that the reciprocal of exposure is usually employed, but at this point in the text "exposure" has not been even mentioned, nor its symbol, R, identified. In any case, the use of R/cm^2 is totally meaningless nonsense.

(4) In the discussion of attenuation of radiation, the amount is stated to be "characteristic of the material" but no mention is made of the dependence on atomic number and density.

(5) The graph which shows the effect on the radiation spectrum of increasing amounts of filtration is misleadingly optimistic. An ideal filter in which the higher energy end of the spectrum is completely unattenuated appears to have been discovered—if only this could be true!

(6) The purpose of the various filters in a film badge (holder) is to make possible an estimation of the quality/type of radiation and not, as the author states, to extend the exposure range. The curious statement that "Records of individual and cumulative exposures give a measure of protection, particularly for long-term effects" demonstrates either careless writing or a dangerously naive appreciation of the subject.

(7) In the one-page discussion of the biological effects of radiation, it is stated: "The threshold of damage is difficult to estimate because the general background of radiation produces effects that are nearly the same as those caused by X-radiation. We can, however, give some general indication of when we would expect radiation associated illness for radiation received over a short time. Up to around 50 rd a person should feel no effects of radiation though damage has been done that in a healthy person would be repaired by the body with no external manifestations". In so far as this means anything it is a most misleading, irresponsible and potentially dangerous statement; the offence of which is not mitigated by the quotation in an earlier table (but without any discussion in the text) of the ICRP maximum permissible dosage values.

The attempt to cover in such a short text this wide range of subject matter is misguided and doomed to failure from the start. The fact that, on the evidence of the text, the author appears to have little familiarity with the practice of the subject does not ease the problem. It is impossible to recommend this book to either the private reader or to libraries.

J. B. Massey.

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Recent Advances in Clinical Nuclear Medicine

William R. Greig, M.D., Ph.D., F.R.C.P., Senior Lecturer in Medicine and Honorary Consultant Physician, The University Department of Medicine and The Department of Nuclear Medicine, Royal Infirmary, Glasgow.

Frank C. Gillespie, B.Sc., Ph.D., F.Inst.P., Principal Physicist, Department of Clinical Physics and Bio-Engineering, West of Scotland Health Boards, Glasgow.

1975 Number One 240 pages illustrated £7·50.

In providing *Recent Advances in Clinical Nuclear Medicine*, the authors have selected some areas in which there have and will no doubt continue to be, evolutionary developments. The essays have been written by experts and though the subjects are diverse the book will be useful to those engaged in all or some aspects of nuclear medicine.

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The Dispensing of Radiopharmaceuticals; Clinical Uses of Cyclotron-produced Radionuclides; Organ Visualisation and Related Studies—Clinical Value; Investigation of Thyroid Diseases; Labelled Fibrinogen in the Study of Deep Venous Thrombosis; Radioimmunoassay; Analysis of Radionuclide Kinetic Data; Organisation of the Specialty of Nuclear Medicine.

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Printed in Great Britain by Lund Humphries
London and Bradford
Published by The British Institute of Radiology
32 Welbeck Street, London W1M 7PG

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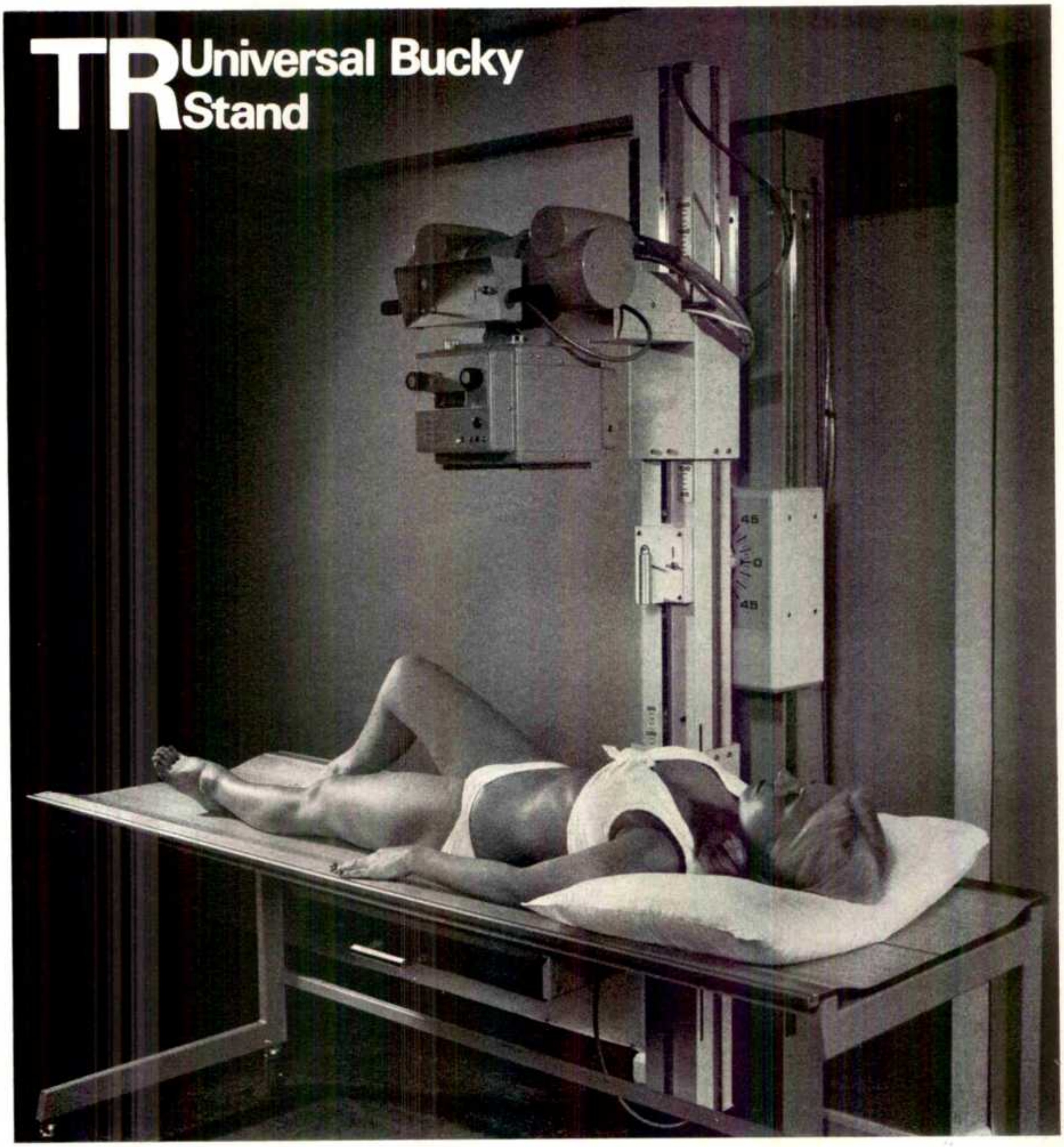

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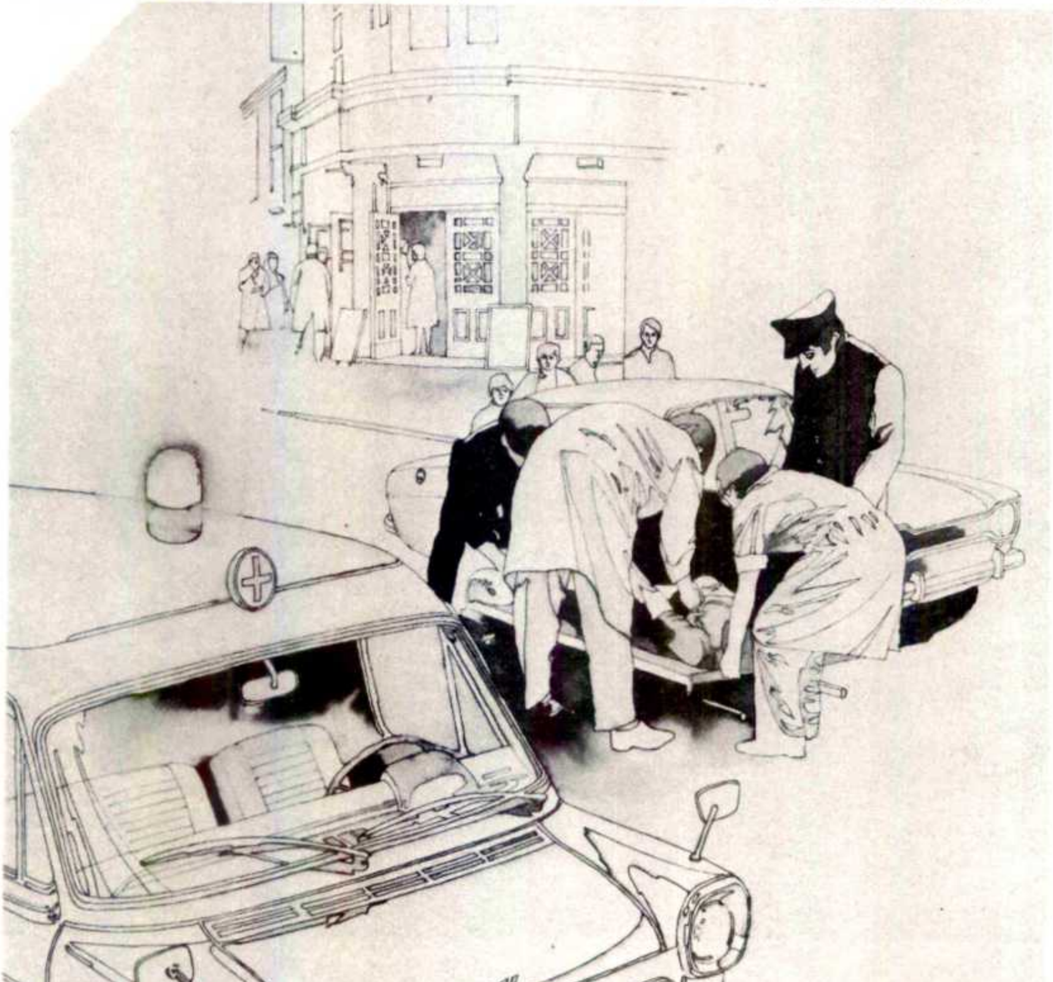

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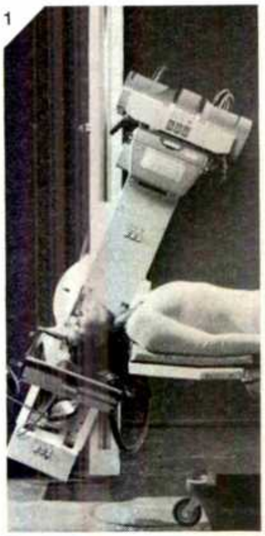

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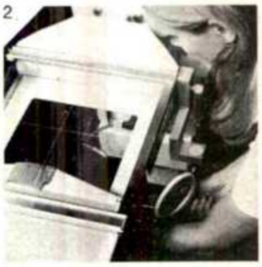

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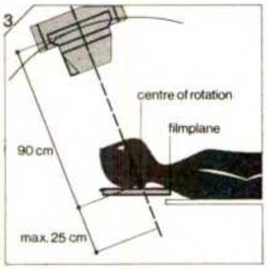

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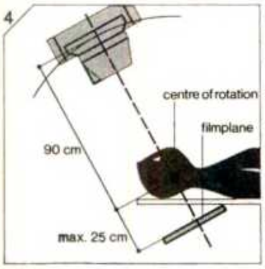

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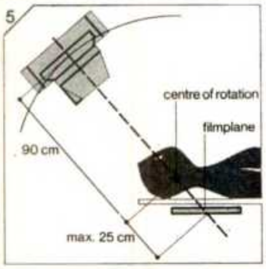

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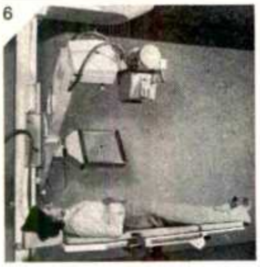

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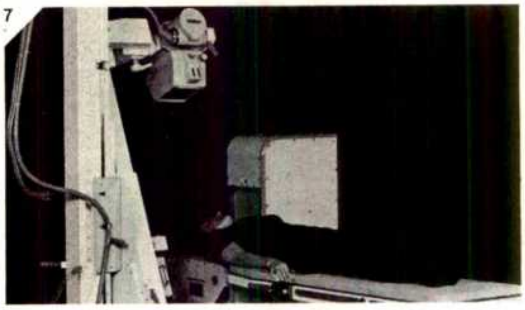

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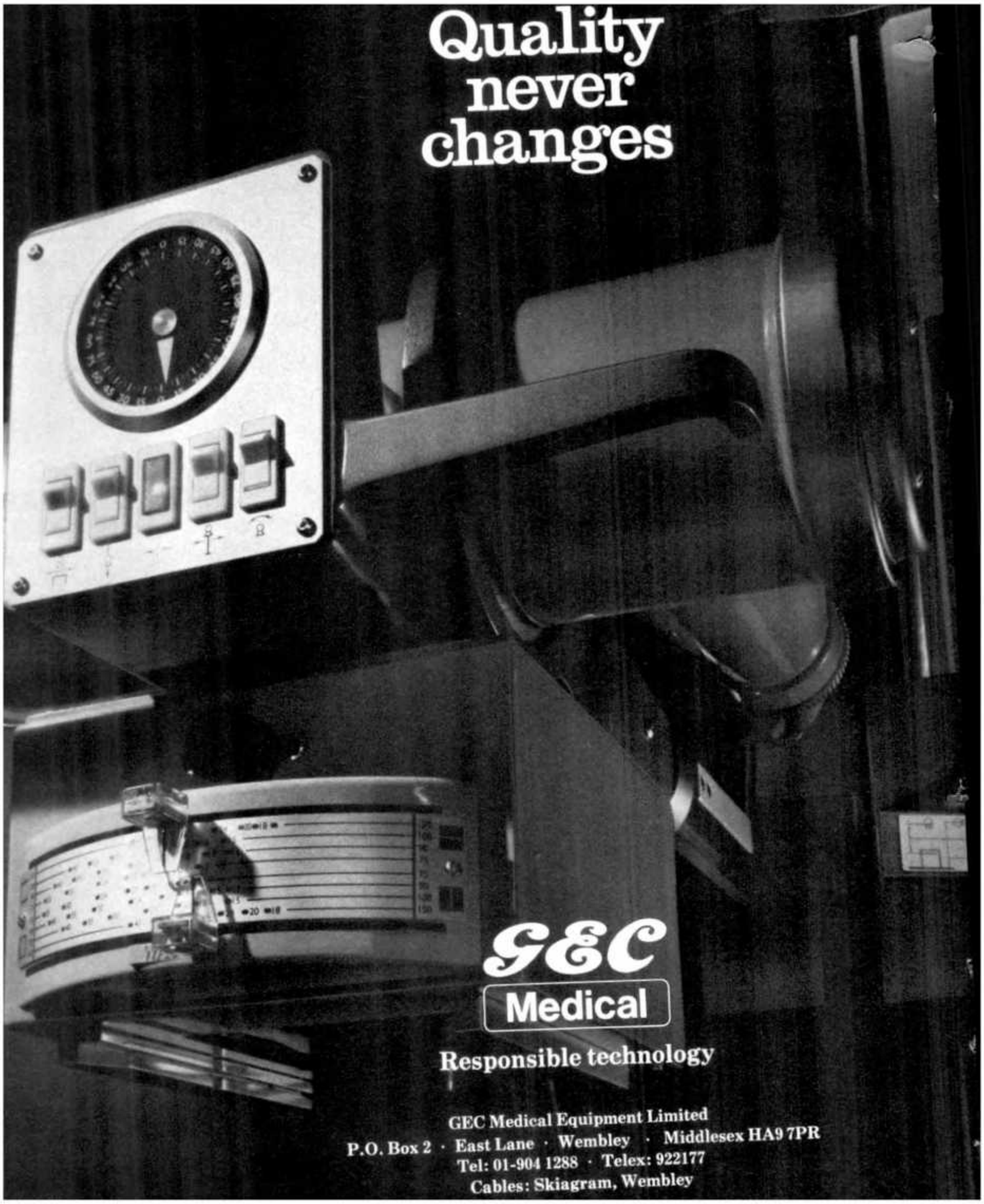

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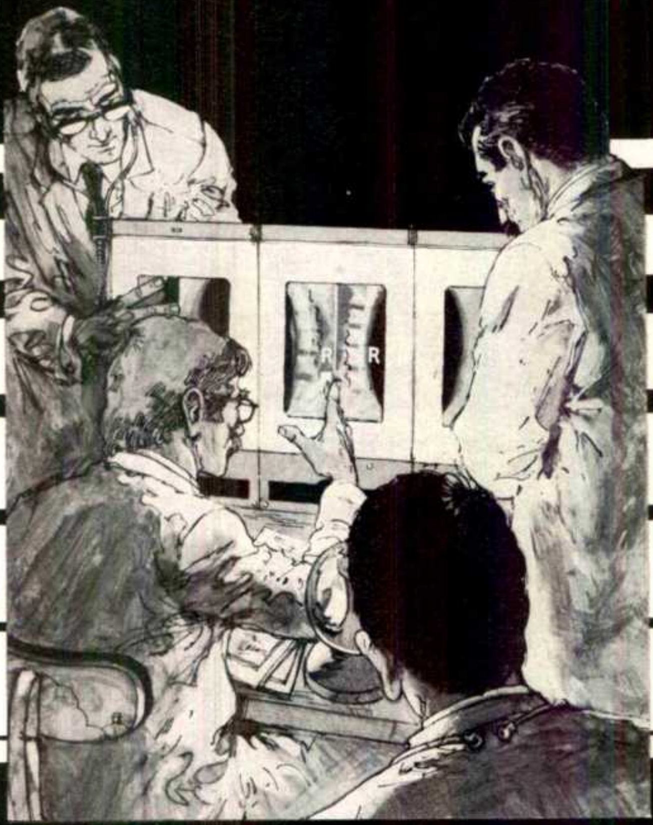

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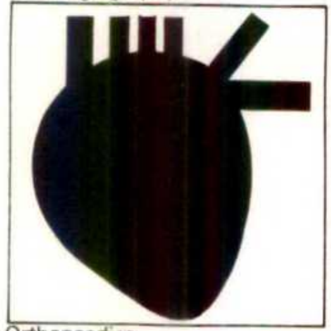

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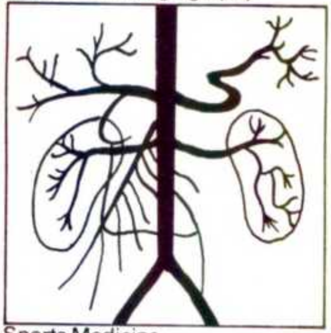

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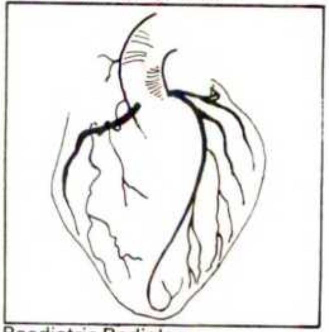

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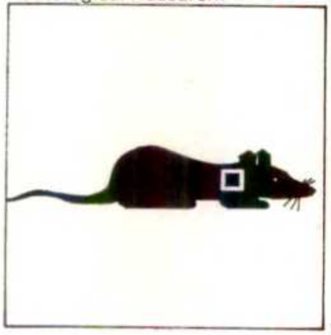

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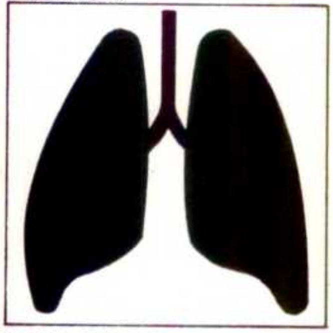

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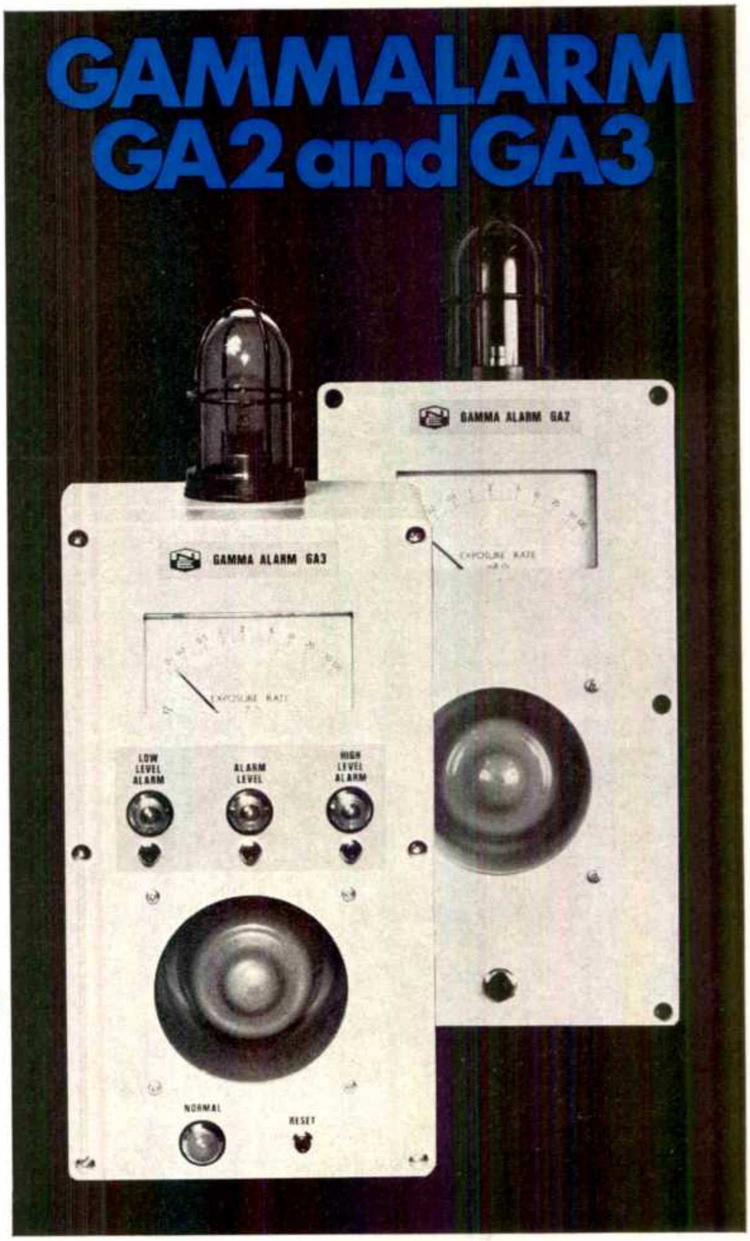

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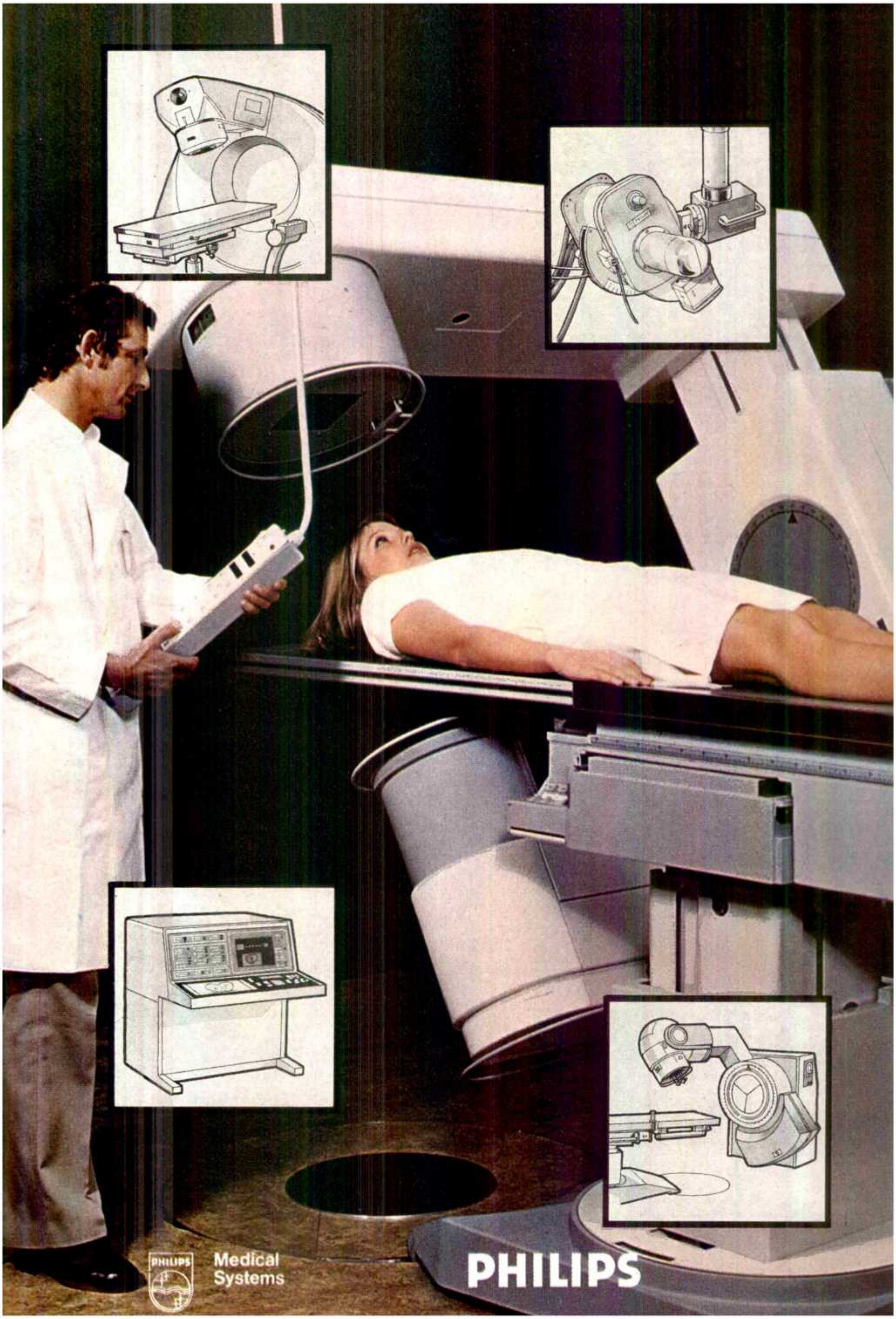

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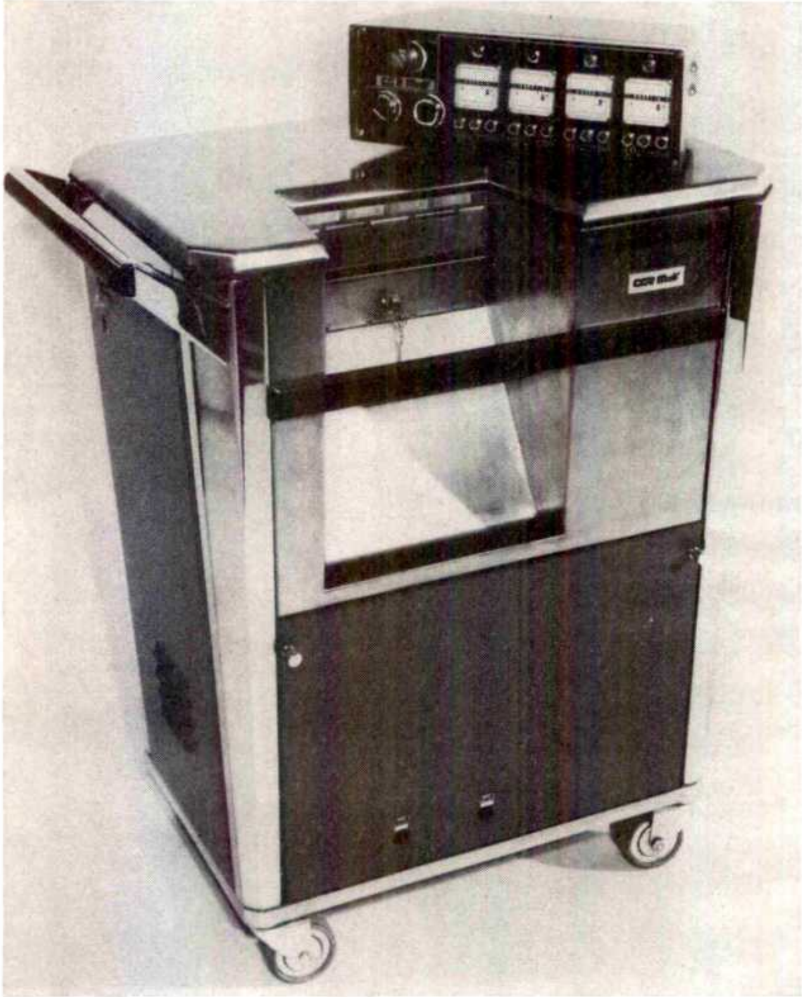

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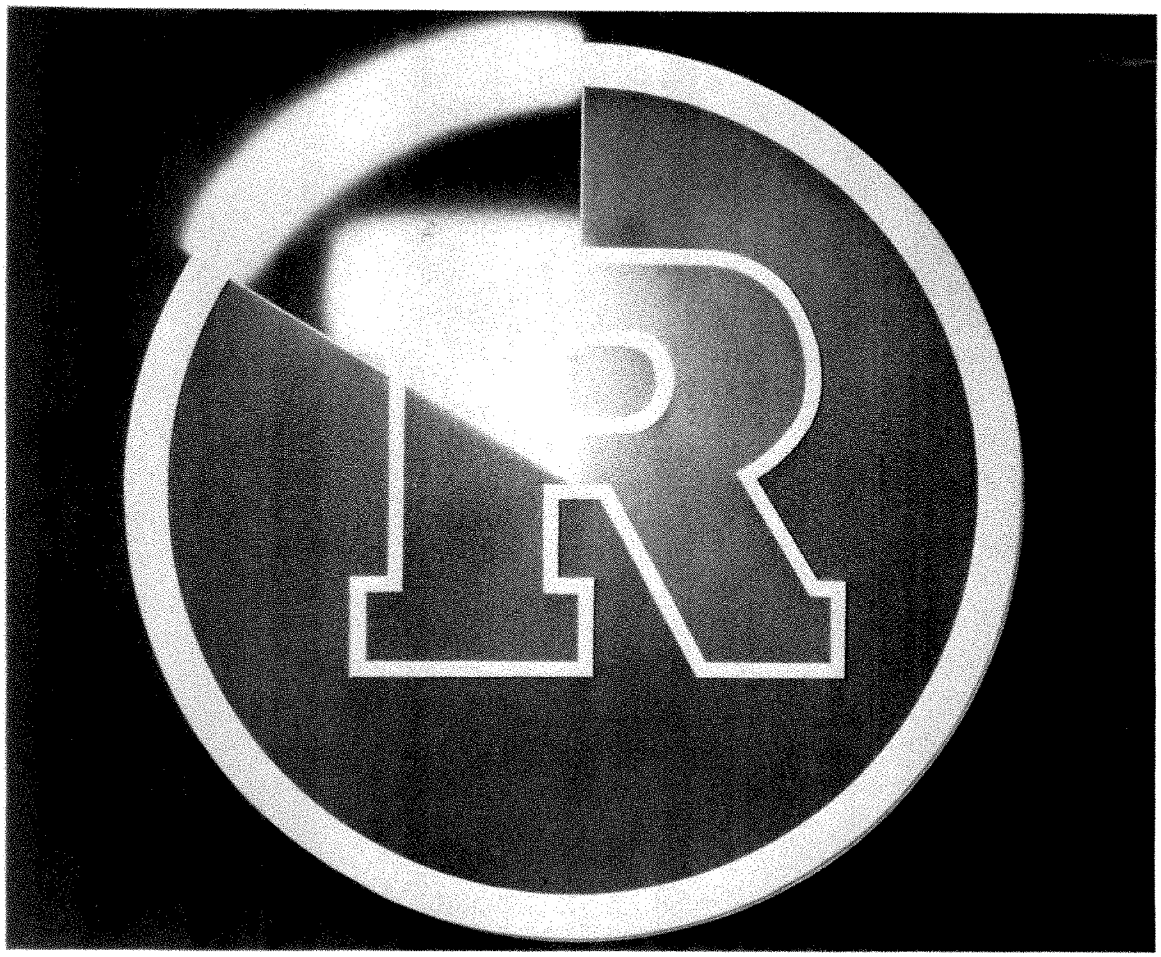

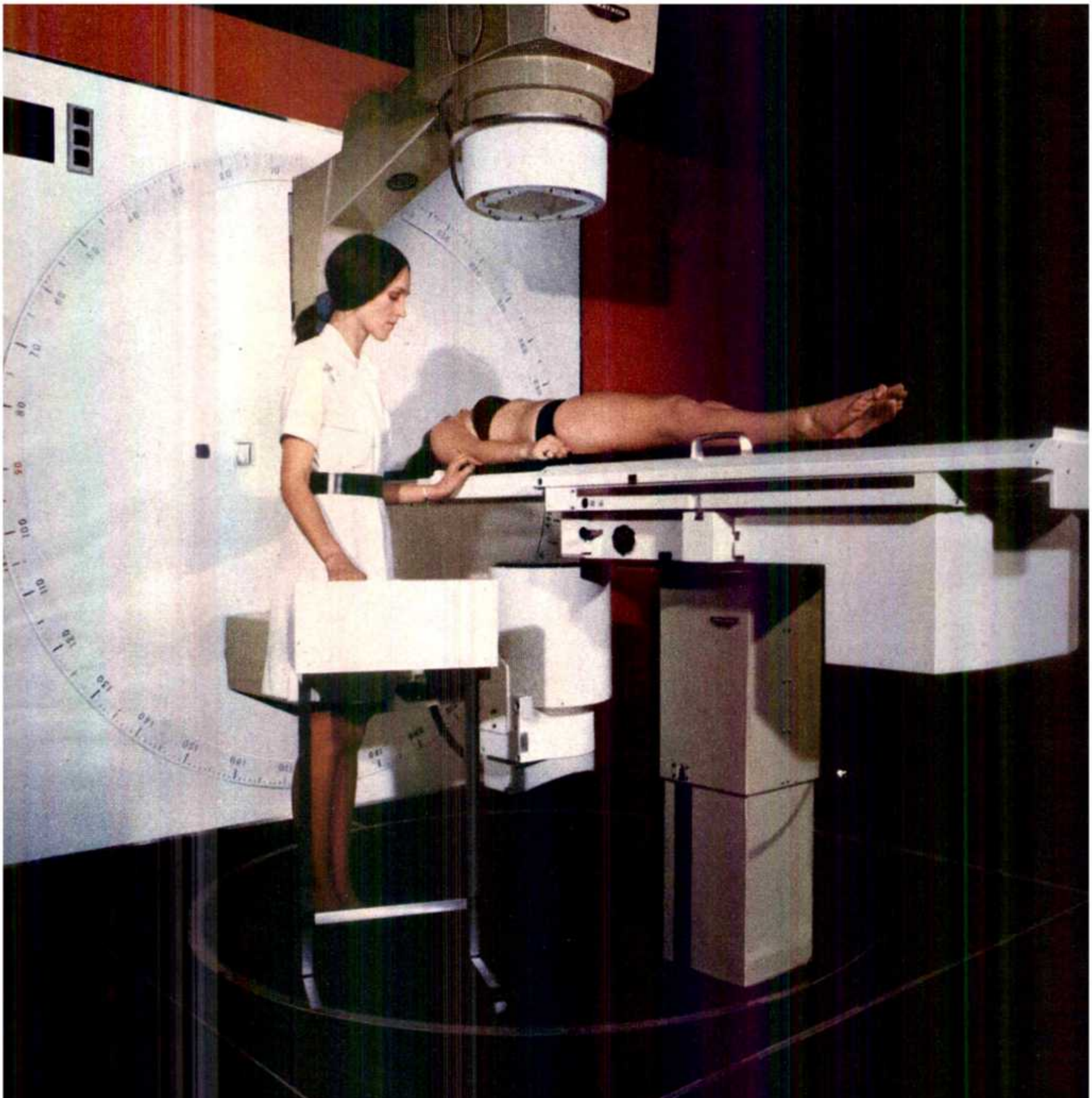

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have reached an agreement giving Siemens the right to market the Ximatron treatment planning simulator, developed and manufactured by TEM.

TEM will continue to sell their range of therapy products throughout the world, and in the UK including the Ximatron.

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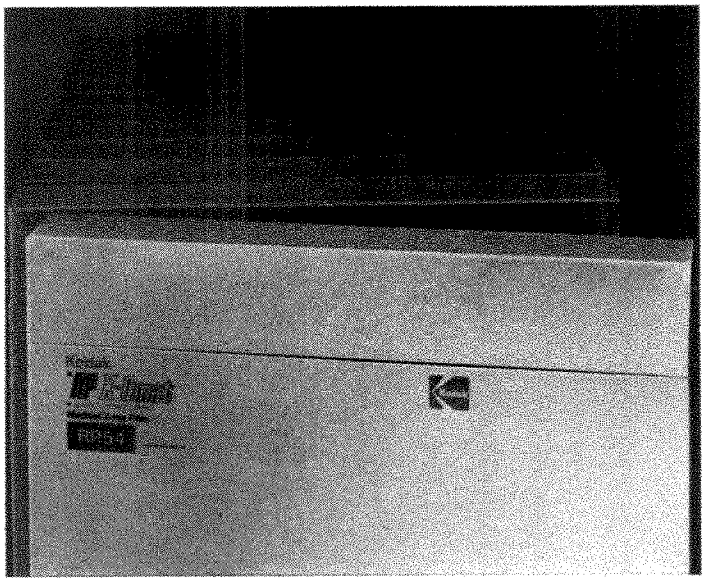

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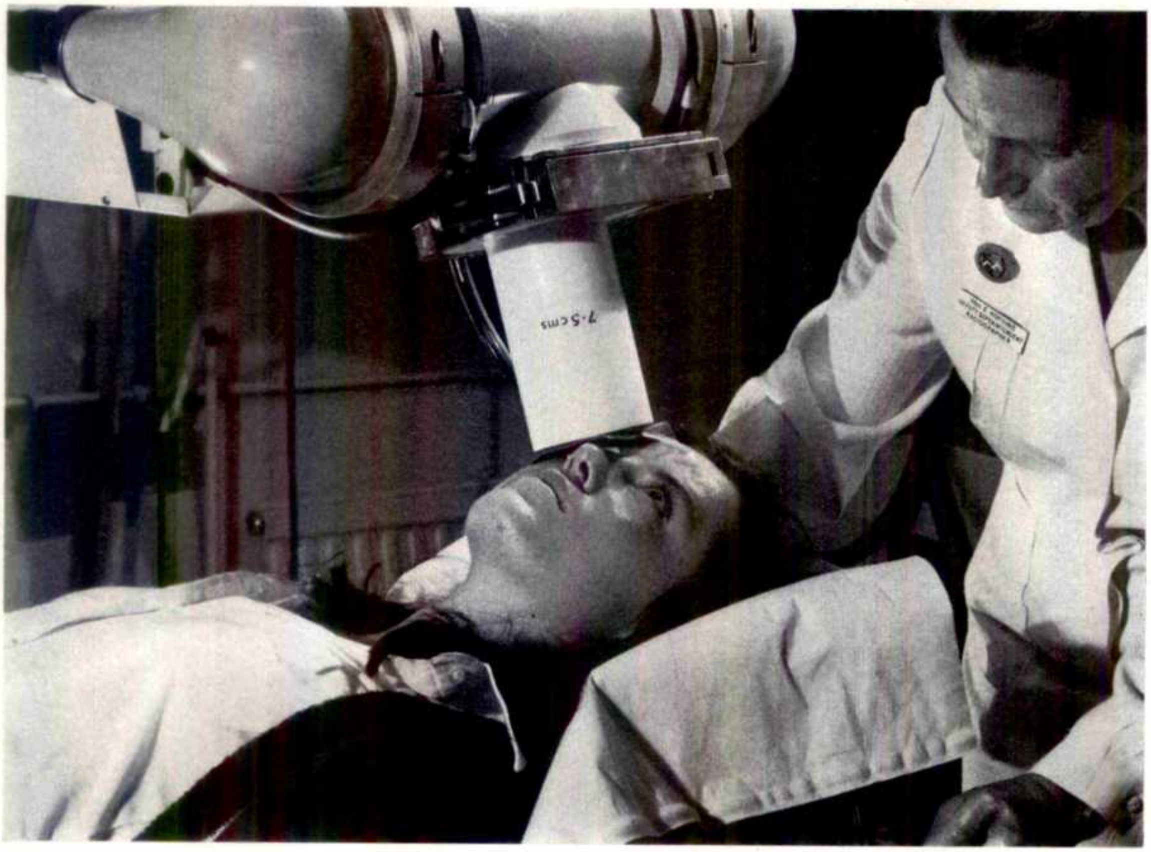

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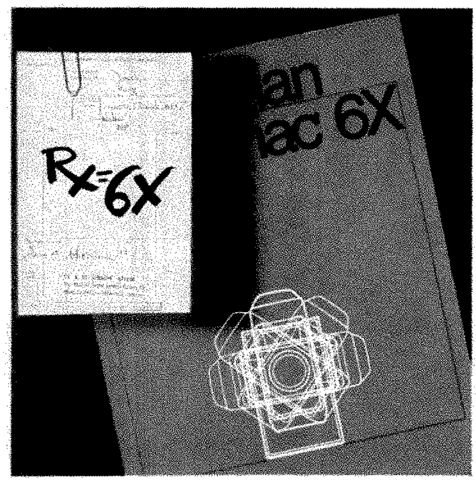

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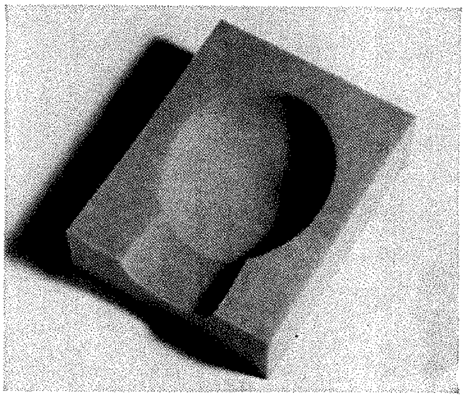

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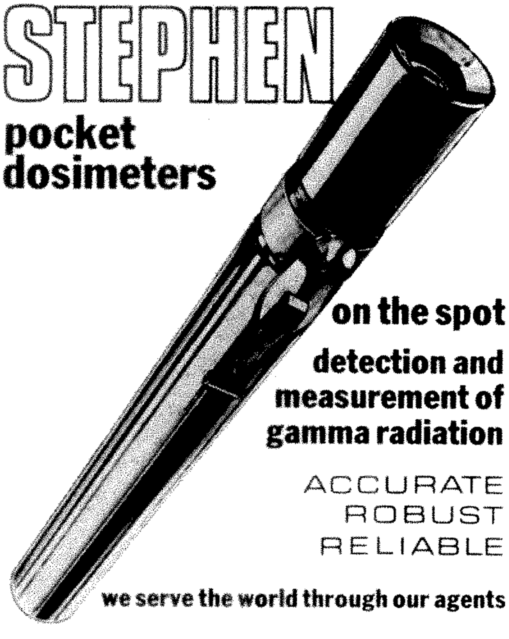

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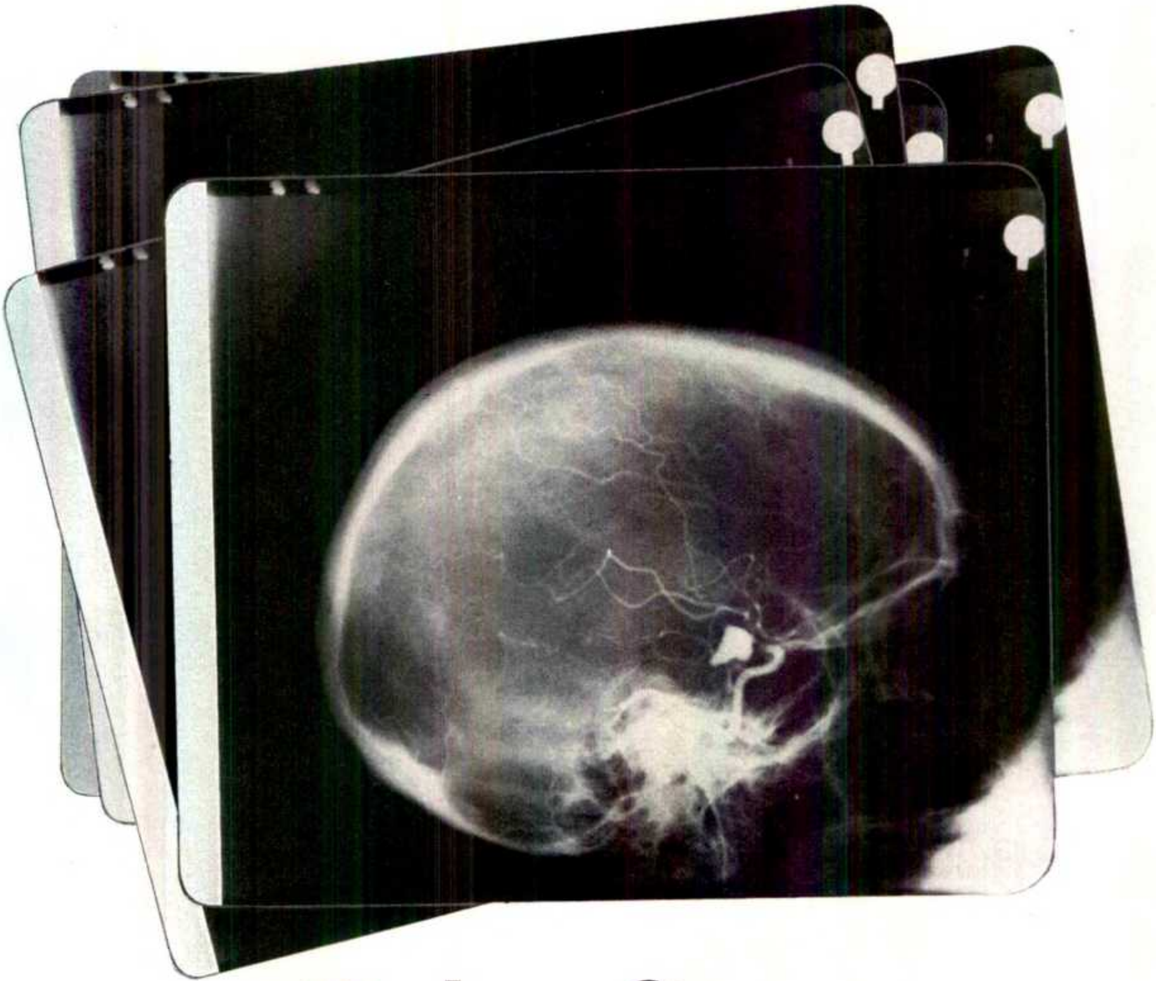

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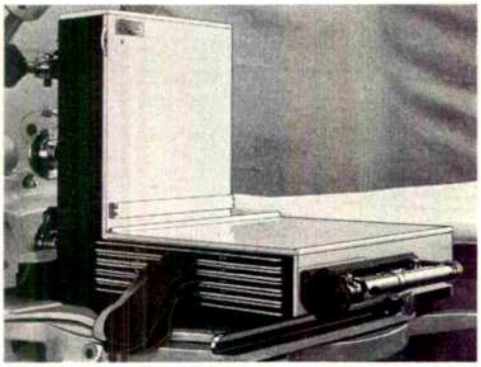

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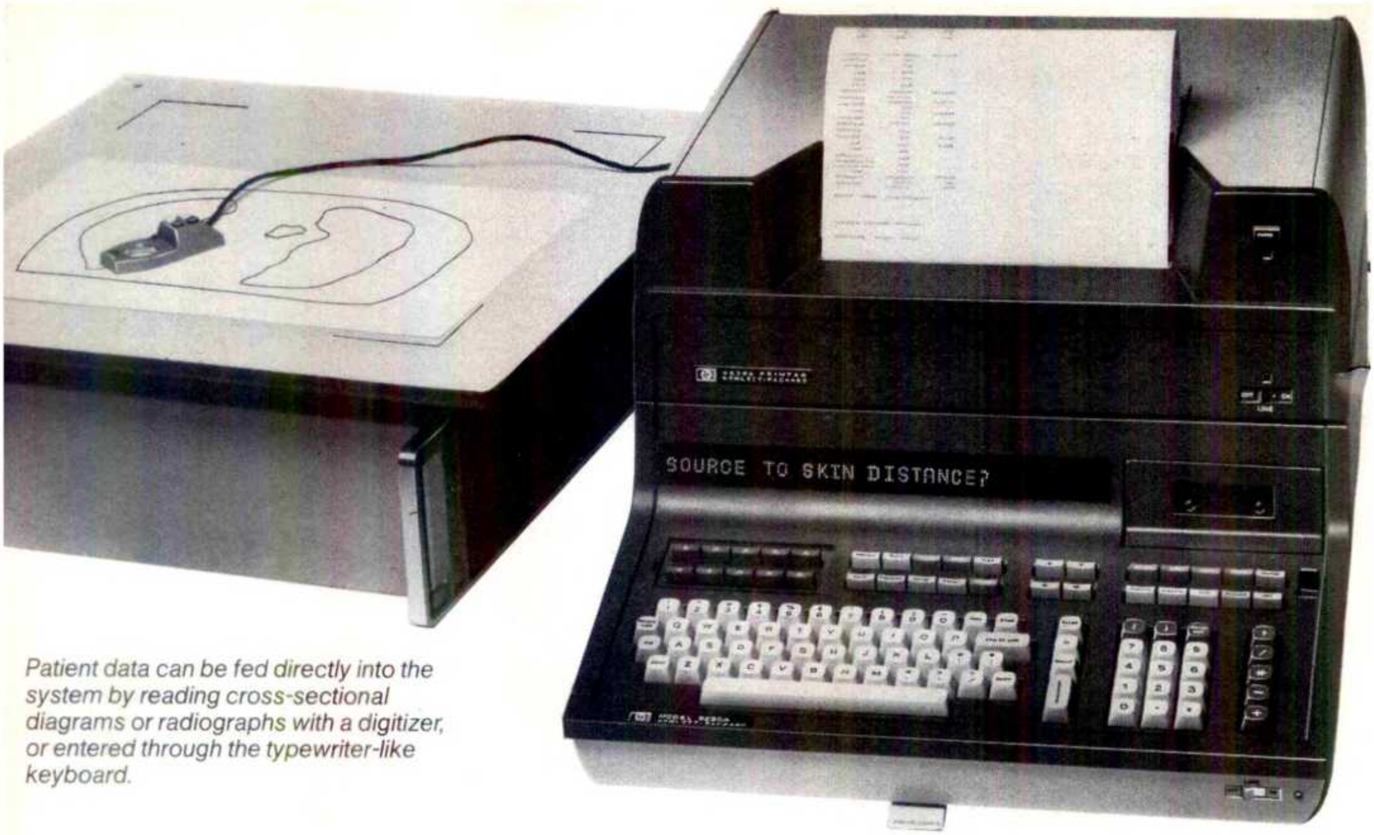

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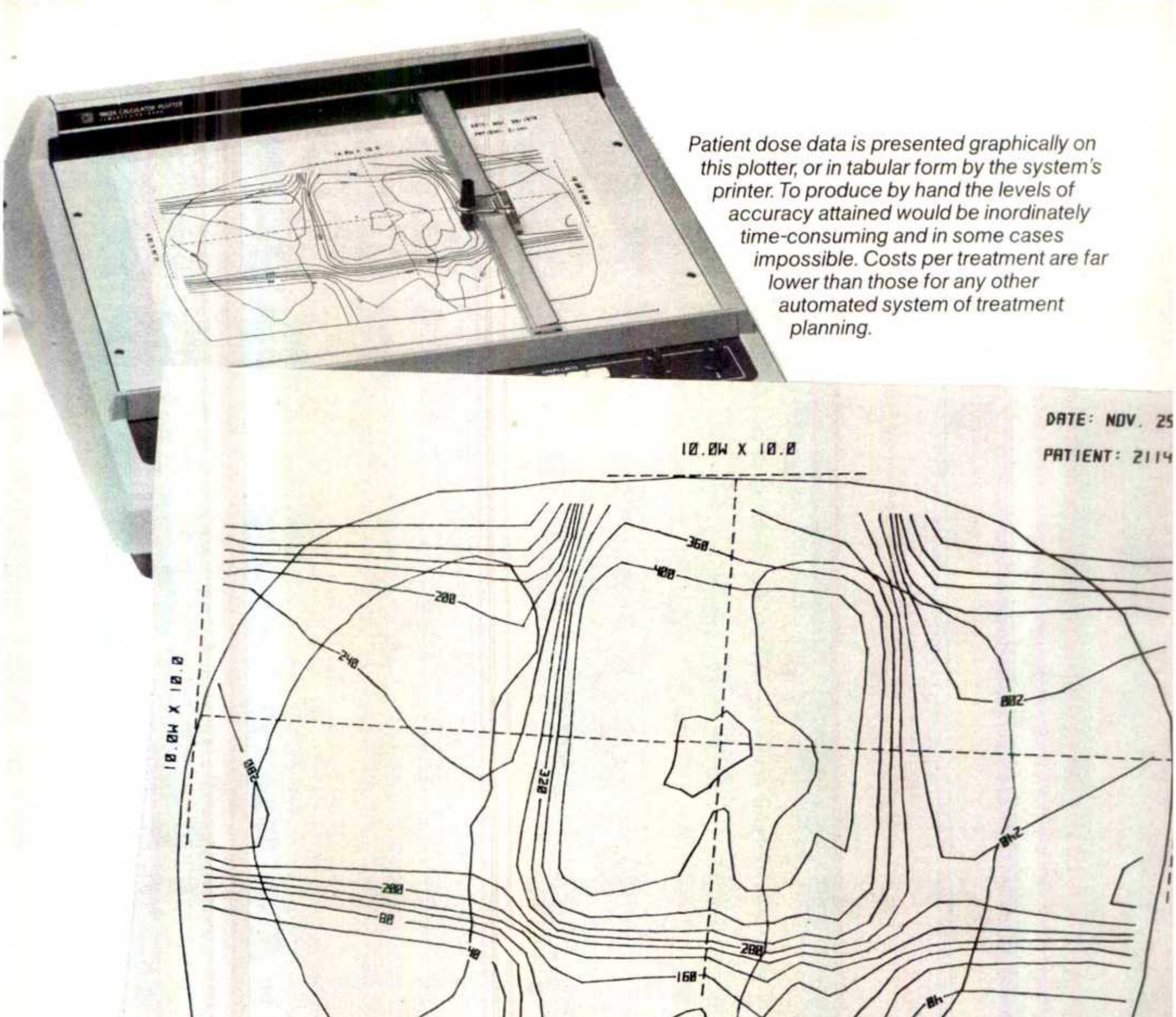

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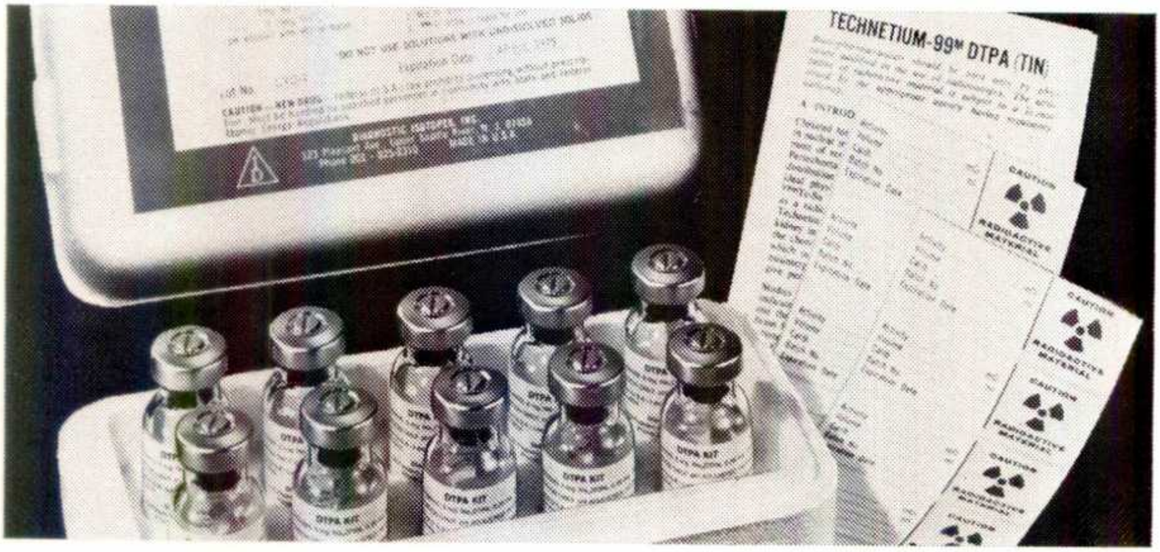

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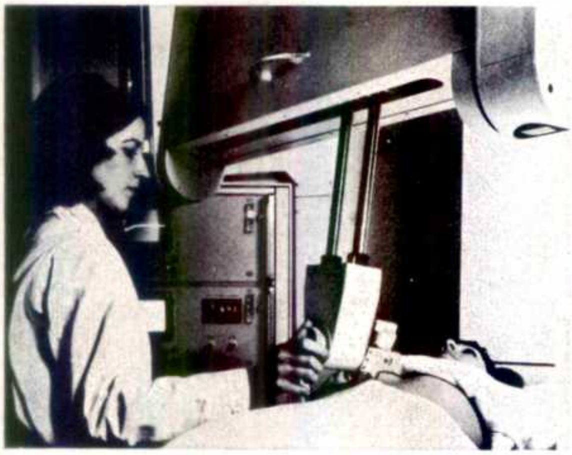

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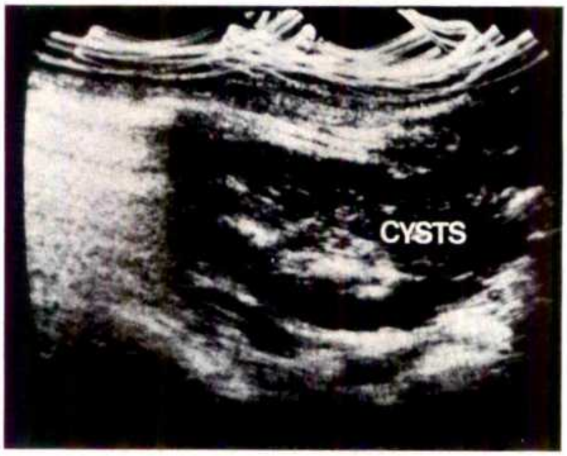

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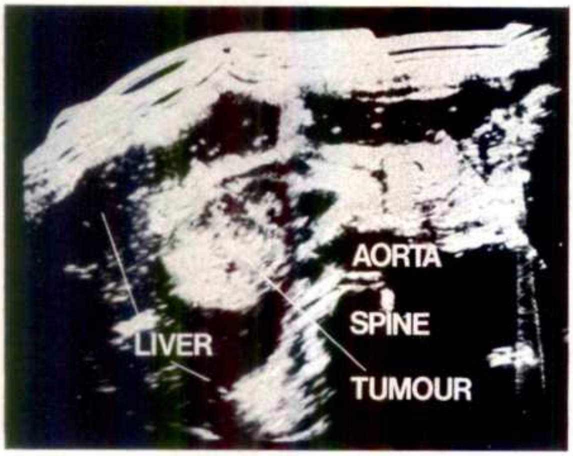

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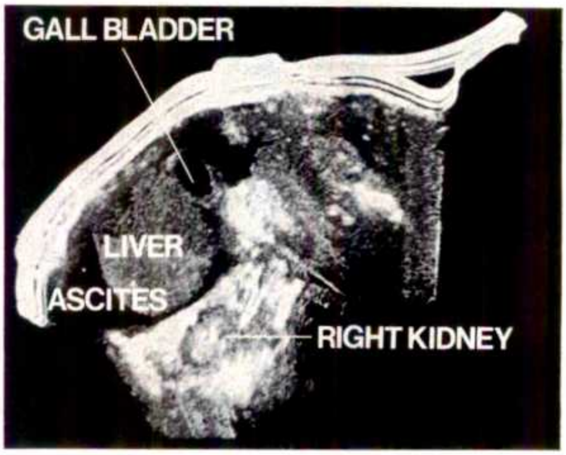

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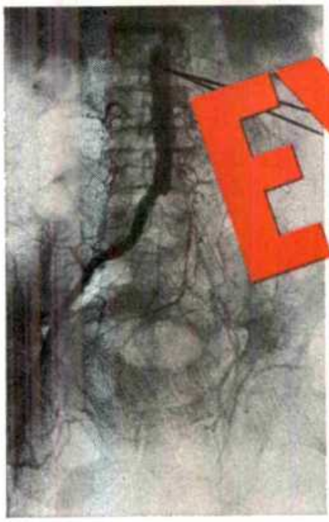

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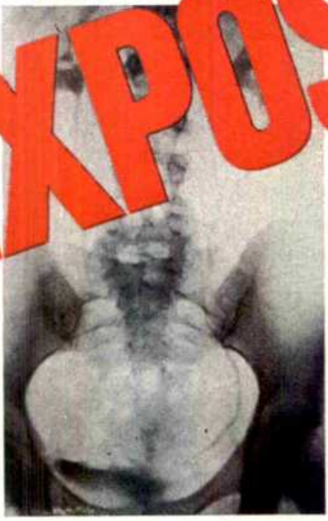

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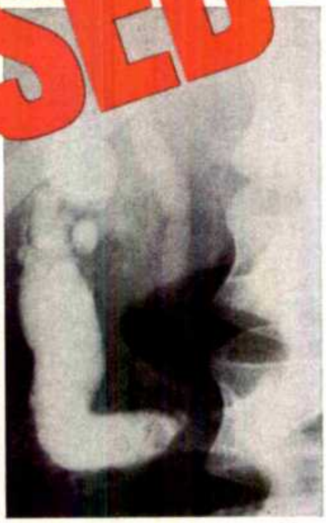

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1976, *British Journal of Radiology*, *49*, 303–305

VOLUME 49 NUMBER 580 APRIL 1976

The British Journal of Radiology

Radiology now

The colon pacified*

It is common practice to give an anticholinergic drug during barium enema examination when it is difficult to fill the colon because of spasm, incontinence or some other reason. In 1958 Welin recommended the routine use of *atropine* by mouth 30 minutes before the examination in order to reduce mucus secretion and alleviate the discomfort of the examination.

Another more powerful anticholinergic drug, *propantheline bromide* (*ProBanthine*) was a common favourite for the relief of colonic spasm (Ferrucci and Benedict, 1971), but side effects proved troublesome. Dilatation of the pupils with loss of accommodating power causing blurred vision is common, often lasting for several hours and sometimes for as long as one to three days. For this reason *hyoscine butylbromide* (*Buscopan*) has become more popular, because prolonged blurring of vision is rare and other side effects are less of a problem. There is also a risk of precipitating glaucoma with these drugs, but one is only likely to run into trouble in patients prone to episodes of closed angle glaucoma. Symptoms of this condition are painful attacks of blurred vision, accompanied by haloes around lights. The effects of hyoscine may be enhanced by concomitant administration of other drugs with parasympatholytic properties, such as some antihistamines, phenothiazines and the tricyclic antidepressants. In these circumstances, and in the presence of ischaemic heart disease or prostatic enlargement Buscopan is best avoided. Notwithstanding this apparently formidable list of contra-indications Buscopan has been extensively used in hypotonic examinations of the gastrointestinal tract, and with few exceptions has proved to be relatively harmless (Herxheimer, 1972; Herxheimer and Haefeli, 1966; Martindale, 1972).

Another drug used for hypotonic duodenography and the double contrast barium meal is *Glucagon*. It has been advocated recently for hypotonic examination of the colon (Gohel *et al.*, 1975; Meeroff *et al.*, 1975 and Miller *et al.*, 1974). Glucagon is produced by the α cells of the islets of Langerhans in the pancreas, and causes an increase in blood glucose concentration by converting liver glycogen to glucose. Its mode of action in relaxing smooth muscle tone is unknown. Glucagon is generally considered to be free of unwanted side effects, but it should not be given to patients with suspected insuloma, or phaeochromocytoma, as it may provoke severe hypertension. Glucagon may also potentiate the hypoprothrombinaemic action of coumarin derivatives, and great caution should be observed before Glucagon is administered to patients receiving anticoagulant therapy (Pannekoek, 1972). As sensitization to Glucagon is a possibility it is inadvisable to give this drug to diabetics.

At the end of the day there are three questions to be answered about the use of hypotonic drugs in barium enema examination:

Q.1 Are hypotonic drugs helpful or are they an inconvenient, expensive and a potentially dangerous waste of time?

A.1 There is no doubt that in certain circumstances hypotonic drugs are helpful:

(1) In some patients distension of the rectum and colon is uncomfortable, and an antispasmodic alleviates this discomfort.

(2) Especially in some elderly patients there is functional inability to retain the barium. In most cases administration of an antispasmodic drug enables the whole of the large bowel to be filled with barium and air with less discomfort to the patient, and without recourse to the potentially dangerous rectal balloon catheter.

(3) Diverticular disease with sigmoid spasm produces pain and discomfort, often with incontinence, and prevents filling of the proximal bowel. An antispasmodic drug helps to overcome this and enables the whole of the large bowel to be demonstrated. In fact Glucagon has been used with success in the treatment of acute diverticulitis (Daniel *et al.*, 1974). Relaxation of the

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*Reprints from: Dr. K. C. Simpkins, Department of Radiology, The General Infirmary, Leeds LS1 3EX.

inflamed sigmoid colon also assists in the differentiation of diverticulitis from carcinoma, and better distension in diverticular disease enables exclusion of any additional lesion such as a neoplasm.

(4) Areas of localized narrowing due to underfilling or spasm simulate carcinoma or other lesions, and the administration of an antispasmodic can resolve this problem.

(5) The use of antispasmodics has been advocated in the barium enema examination of inflammatory bowel disease (Miller *et al.*, 1974). Undoubtedly discomfort and pain limit filling and distension in some patients with colitis. It is tempting to give antispasmodics to ease the patient and achieve a better demonstration of the abnormal bowel. However, these symptoms are danger signals against further distension, with the risk of perforation of a thin and inflamed colon. There is also in acute colitis a danger of precipitating toxic megacolon by giving an anticholinergic or other hypotonic drug (Korelitz, 1975). In acute colitis, therefore, drugs should be used with extreme caution, and only in those patients where there is some particular problem such as suspected malignant change. In these circumstances Glucagon is probably less dangerous than the anticholinergic drug Buscopan.

The short duration of action of these drugs enables after-evacuation films to be obtained in the usual way. Filling of the terminal ileum may be facilitated (Miller *et al.*, 1974), but this is not likely to be a significant factor. In the presence of an obstructing lesion, barium should not be allowed to overfill the proximal colon during a hypotonic enema because reduction of muscle tone could permit an incomplete obstruction to become total (Ferrucci and Benedict, 1971).

Q.2 Should hypotonic drugs be used selectively or routinely in all cases?

A.2 The routine use of a drug in any individual diagnostic procedure in radiology should only be advocated if it is essential for diagnostic quality or the patient's comfort. For example, a hypotonic agent is essential for hypotonic duodenography, but this does not apply to the barium enema. Most patients, perhaps three out of four, do not experience undue discomfort, and most lesions can be clearly seen and maximum information obtained without recourse to drugs. It is therefore unnecessary to administer a potentially dangerous drug to every patient. Nevertheless there should be no hesitation in giving a hypotonic drug when it is of benefit.

Q.3 Which is the most effective, most convenient and least harmful agent, and what contraindications and precautions should be observed in its use?

A.3 The choice is between Buscopan and Glucagon. Both drugs are given by intravenous or intramuscular injection, but Buscopan is more convenient as it is supplied as a solution in a vial ready for injection, whereas Glucagon requires mixing of powder and solvent before administration. Both have rapid effect when injected intravenously, and after about five minutes when given intramuscularly. The duration of action of both is about 15 minutes. Both drugs are believed to be equally effective, but there has been no comparative trial of their action on the colon. Spasm and irritability of the bowel with consequent discomfort to the patient and incontinence occasionally persist after giving either Buscopan or Glucagon in their usual doses, and larger amounts such as 60 mg I.V. Buscopan or 2 mg I.V. Glucagon may occasionally be required.

Glucagon is the least harmful agent except to those with an insuloma or phaeochromocytoma, or on anticoagulants. Buscopan should be avoided in those who expect to drive a vehicle or operate machinery within an hour of the injection, and patients given Buscopan should be warned of its possible visual effects. Buscopan should not be given to those who admit to attacks of visual disturbance with pain, to elderly men with a history of prostatic enlargement, or in ischaemic heart disease. Both drugs should only be given with great care to those who have taken any medication within the previous 14 days.

In order to take account of all these possibilities it is suggested that each patient, with the help of a nurse or radiographer, fills in a proforma of relevant questions before coming into the X-ray room so that the radiologist can see at a glance which drug is appropriate. In those cases where none of these clinical limitations apply Buscopan (at 7p for 20 mg) is to be preferred to Glucagon (at £1·59 for 1 mg) on account of ease of administration and cost.

K. C. SIMPKINS

REFERENCES

DANIEL, O., BASU, P. K., and AL-SAMARRAE, H. M., 1974. Use of Glucagon in the treatment of acute diverticulitis. *British Medical Journal*, *3*, 720–722.

FERRUCCI, J. T., and BENEDICT, K. T., 1971. Anticholinergic-aided study of the gastrointestinal tract. *Radiologic Clinics of North America*, *Vol. IX*, *No.1*, 23–36.

GOHEL, V. K., MURRAY, K. D., and COREN, G. S., 1975. Hypotonic examination of the colon with Glucagon. *Radiology*, *115*, 1–4.

HERXHEIMER, A., 1972. Atropine-like drugs–in side effects of drugs. In *Excerpta Medica*, edited by L. Meyler and A. Herxheimer, Vol. 7, Chapter 15, p. 243.

HERXHEIMER, A., and HAEFELI, L., 1966. Human pharmacology of Hyoscine Butylbromide. *Lancet*, *2*, 418–421.

KORELITZ, 1975. Personal communication.
MARTINDALE, 1972. *The Extra Pharmacopoeia, 26th edn.*, p. 273.
MEEROFF, J. C., JORGENS, J., and ISENBERG, J. I., 1975. The effect of Glucagon on barium enema examination. *Radiology*, *115*, 5–7.
MILLER, R. E., CHERNISH, S. M., SKUCAS, J., ROSENAK, B. D. and RODDA, B. E., 1974. Hypotonic colon examination with Glucagon. *Radiology*, *113*, 555–562.
PANNERDEK, J. H., 1972. Insulins Glucagon and oral hypoglycaemic drugs – in side effects of drugs. In *Excerpta Medica*, edited by L. Meyler and A. Herxheimer, Vol. 7, Chapter 41, p. 581.
WELIN, S., 1958. Modern trends in diagnostic roentgenology of the colon. The Mackenzie Davidson Memorial Lecture. *British Journal of Radiology*, *31*, 453–464.

Book review

Encyclopedia of Medical Radiology, Vol. X, Part 2b. *Roentgen Diagnosis of the Heart and Blood Vessels.* Edited by L. Diethelm, F. Heuck, O. Olsson, K. Ranniger, F. Strnad, H. Vieten and A. Zuppinger, 1974 (Berlin, Heidelberg, New York, Springer-Verlag), $137.10.

This new volume of the *Encyclopedia of Medical Radiology* covers only a small part of disease of the heart and the vascular tree. It comprises a number of chapters written by different authors. There is a section on intracardiac calcifications such as the heart valves and the coronary arteries, and a short chapter on intracardiac thrombi. A comprehensive section on tumours of the heart and pericardium is followed by a short section on parasitic disease of the heart. There is an important chapter on the pathological features and morphology of the coronary arteries, followed by two sections on the radiological features of coronary artery disease and coronary angiography. The latter are the only two sections written in English. In a chapter on so-called "myodegeneratio cordis" due to age, the author discusses a topic which is not familiar to British readers. There is a short chapter on changes of the heart due to arterio-venous communications, as well as a comprehensive chapter on cor pulmonale, a section on hypertension, followed by a short section on the various appearances of the normal heart and its anatomical variations in a new born. In the section on peripheral vascular disease there is a large chapter on diseases of the thoracic aorta, and a shorter section on diseases of the veins of the mediastinum.

Most of the monographs are by no means comprehensive and are often somewhat disjointed, which makes reading sometimes difficult. Some of the material presented is not always up to date, though an attempt is made to include recent developments. The section on myocardial degeneration is unusual and not very convincing, and the chapter on cor pulmonale is equally difficult to understand, since the appearances of cor pulmonale in obstructive airways disease and pulmonary hypertension due to other causes are not too clearly defined and separated.

There are a large number of negative reproductions in the text, not commonly used in the English literature. Some of the angiograms are not of a very high standard, and are inadequately annotated due to lack of diagrams and clearer descriptions.

There is a long list of references appended to each chapter; some are out of date, whereas some of the recent ones are missing.

It is very questionable if a book of this kind can ever be up to date, and at the cost of £60 it is unlikely that many individuals will be able to afford it.

R. E. STEINER.

1976, *British Journal of Radiology*, *49*, 306–315

New diagnostic horizons with sonar

By I. Donald, C.B.E., M.D., F.R.C.S. (Glasg)., F.R.C.O.G.*

The Mackenzie Davidson Memorial Lecture given at The British Institute of Radiology, February 20, 1975

(*Received February, 1975*)

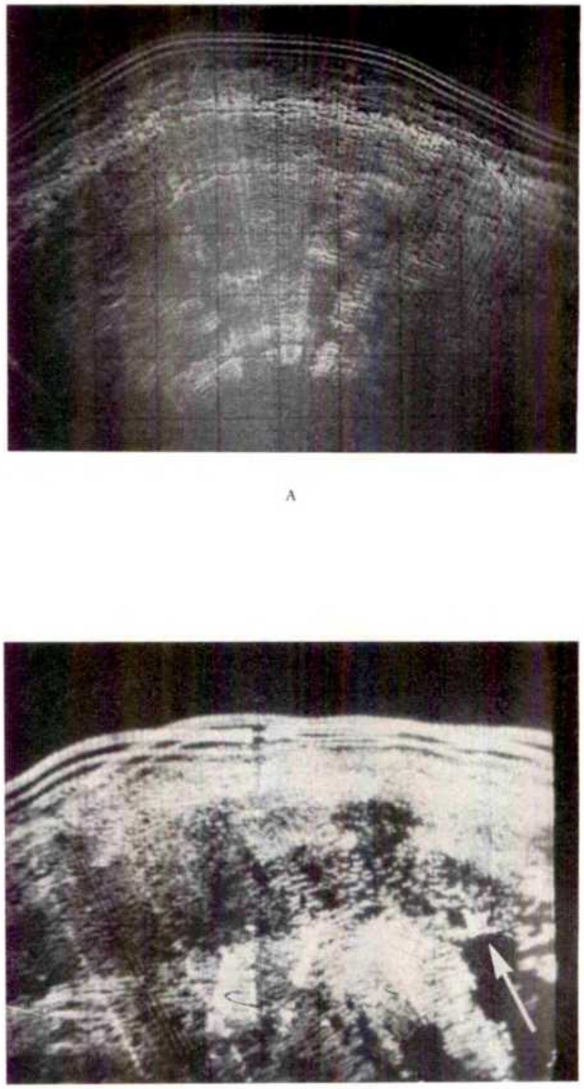
Since Lord Rutherford gave the first lecture in memory of Sir James Mackenzie Davidson in 1920 the list of lecturers who have followed him has included men of science and of medicine who may be counted among the intellectual giants of this century. A simple clinical gynaecologist like myself can hardly contribute significantly to such illustrious memory.

There are two ways of looking at the extending horizons of sonar. One is to take account of the ever-increasing range of applications and the other depends upon the exploitation of fresh technical developments. It is important to recognize not only the scope of the technique but also its limitations. In a quantitative sense, the greatest clinical impact so far has been in the field of obstetrics and with pelvic masses provided in gynaecology. This is where we ourselves started about twenty years ago (Donald *et al.*, 1958) but the subject now has diverse applications including all types of abdominal echography (Barnet and Morley, 1974), ultrasound cardiology, ophthalmology and neurology. A number of very useful volumes have appeared within the past few years which encompass far more material than I could hope to review in a lecture such as this (Barnet and Morley, 1974; Brown and Gordon, 1967; King, 1974; Wells, 1972).

Rather than recapitulate what I and my colleagues in Glasgow have attempted and put forth in very numerous publications, my purpose is to present still newer work arising from a very major advance now applicable to the ultrasonic art. I refer to grey-scale imaging as a breakthrough which may render much of our work of the last two decades out of date.

BACKGROUND

Over many years, especially since the University of Glasgow set up the Department of Ultrasonic Technology based on the Queen Mother's Hospital, our technical research interests have been concerned with improving resolution, refining the accuracy of



A

B

FIG. 1.

Original attempts at grey-scaling technique before availability of scan converter, shows thickened ground glass type of placenta, (A) before treatment by plasmapheresis, (B) after 36 maternal exchange plasmaphereses extending over 13 weeks. Child delivered two days after (B) and although affected by Rh haemolytic disease survived following two exchange transfusions. Intra-uterine transfusions avoided.

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*Department of Midwifery, Queen Mother's Hospital, Glasgow G3 8SH.

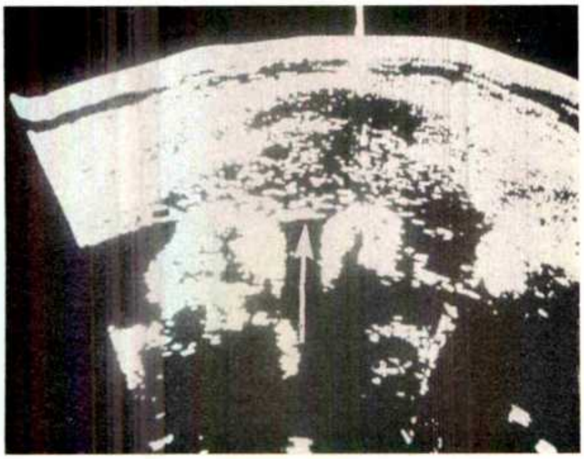

FIG. 2.
A normal placenta by old technique.

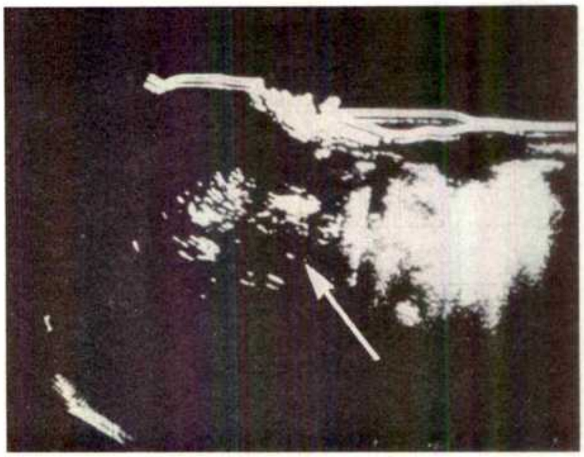

FIG. 3.
Hepatic metastases. Standard technique.

measurement and with energy studies and calculations, three-dimensional display and information retrieval.

Although we have demonstrated the feasibility of three-dimensional holography by a multiplex sonar technique (Donald, 1969), in conjunction with the Atomic Weapons Research Establishment, we have not yet succeeded in making this method of storage and information retrieval economically viable or clinically worth while. Up to a few months ago it appeared that in routine sonar we had reached a plateau in the matter of resolution and accuracy and for a brief while, I did not see how we could improve our technique in spite of my dissatisfaction with it. Meanwhile opportunities abounded in the sheer weight of the clinical material with placentography and in particular biparietal cephalometry still forming the heaviest part of the workload.

Although we are obstetricians and gynaecologists, we are nevertheless interested in diversification and, in collaboration with our radiological colleagues at the Western Infirmary, Glasgow, we gladly seize upon any opportunity of studying other organs. For example, the technique developed by Dr. Ted Lyons in my department for scanning the kidneys in tiny babies using a warm water-bath tank under which they slept peacefully, warmly and happily (Lyons *et al.*, 1972) has now been taken over in full by Dr. Elizabeth Sweet in the neighbouring Royal Hospital for Sick Children.

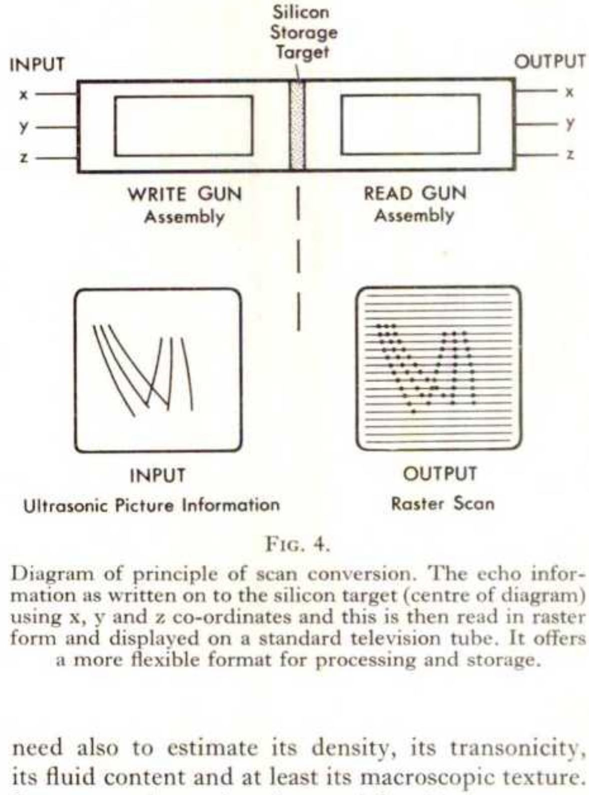

FIG. 4.
Diagram of principle of scan conversion. The echo information as written on to the silicon target (centre of diagram) using x, y and z co-ordinates and this is then read in raster form and displayed on a standard television tube. It offers a more flexible format for processing and storage.

TISSUE STRUCTURAL STUDIES

To recognize the anatomical configuration of an organ or a tumour is not in itself enough. There is need also to estimate its density, its transonicity, its fluid content and at least its macroscopic texture. In no two tissues has the need for this been more evident than in the case of the placenta, which is a very difficult organ to study by any technique *in vivo*, and of the liver. This also applies to a lesser extent to kidneys and spleen.

The need was brought home when, in the course of the past year, a new approach in the management

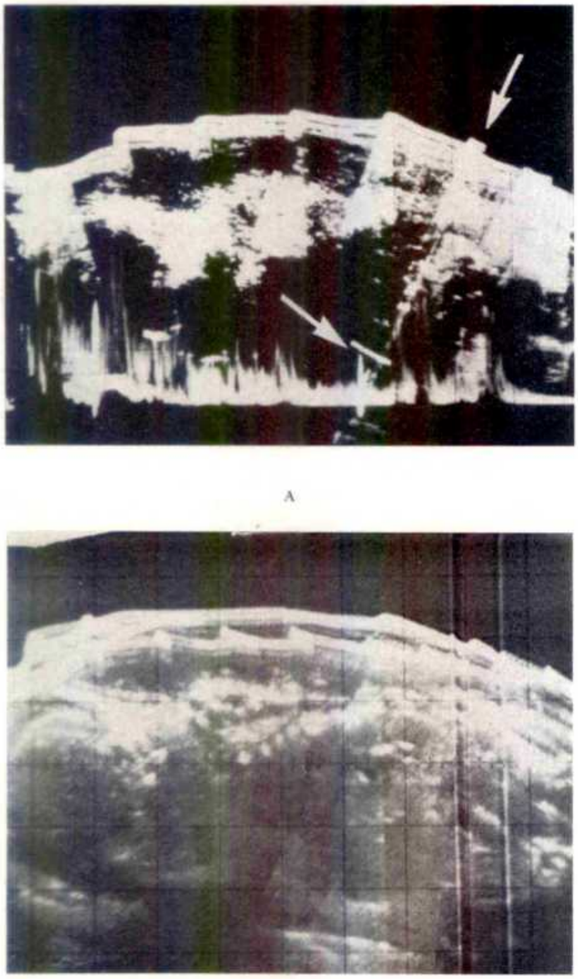
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FIG. 5.

Demonstrates the principle of A-scan and grey-scale imaging. (A) Shows a longitudinal view of a fetal trunk and anterior placenta. Along the bottom of the picture is an A-scan trace, taken with the beam halted in the line of the arrow in the upper right corner. A bewildering profusion of blips in the A-scan trace and of white dots on the B-scan trace. The cursor mark has been superimposed on both (arrow); (B) Grey-scale picture for comparison with older standard technique in (A).

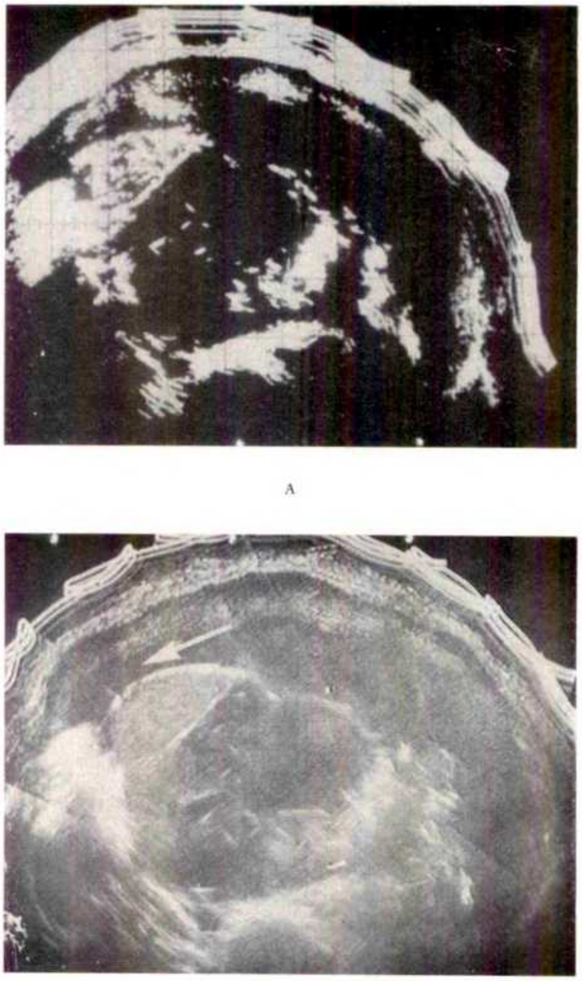
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FIG. 6.

Ovarian carcinomatosis with six litres ascites. Note liver, top left, separated from diaphragm by free fluid. (A) Standard technique, (B) grey scale.

of severe Rhesus haemolytic disease in pregnancy by repeated maternal plasmapheresis became available. The need to study the placenta during such treatment became urgent. We have long recognized (Donald and Abdulla, 1968) that the severely affected Rhesus placenta demonstrates, on sonar examination, a thickened, more opaque ground-glass type of appearance, presumably due to villous oedema.

Hitherto any hope of fetal survival in severe cases has depended upon repeated intra-uterine transfusion until premature delivery could be safely undertaken. This has a high mortality. Such cases are now considered for repeated maternal plasmapheresis, two or three times a week for months on end, to remove the maternal antibodies by means of a cell separator and to exchange her plasma for

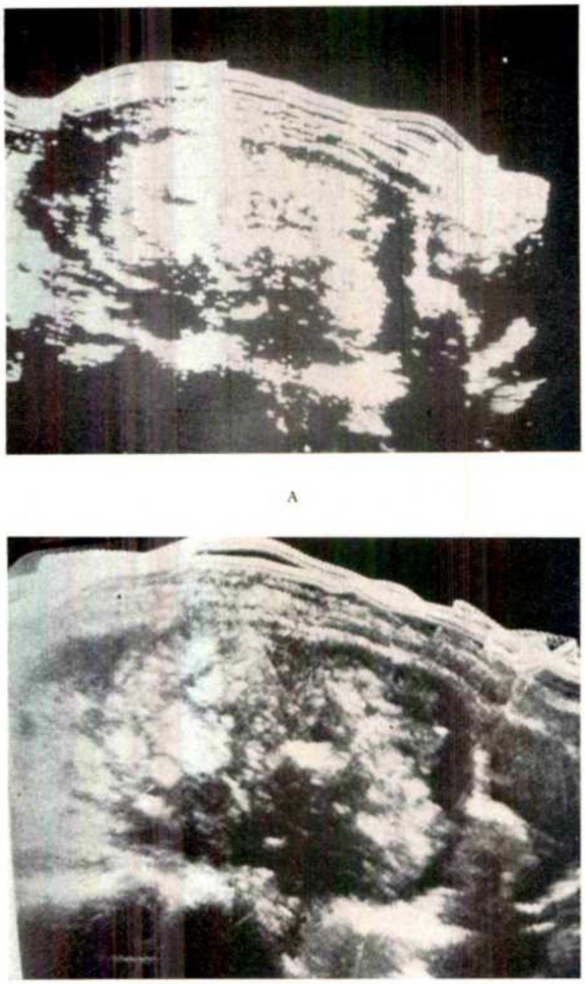

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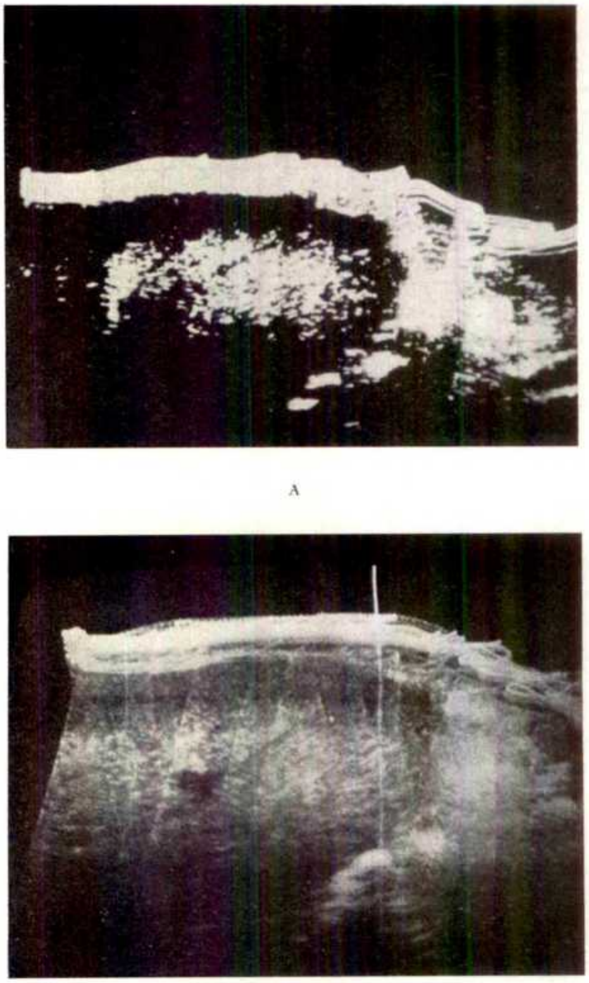
FIG. 7.

Massive malignant ovarian teratoma, (A) standard technique; (B) grey scale.



A

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FIG. 8.

Gross hepatomegaly due to diffuse alcoholic cirrhosis. Note diffuse echo pattern, (A) standard; (B) grey scale technique.

donor plasma. We are naturally interested to see what effect such treatment can have upon the placenta itself and to match the changes with those which can be observed on repeated amniocentesis and spectrophotometry of the liquor amnii.

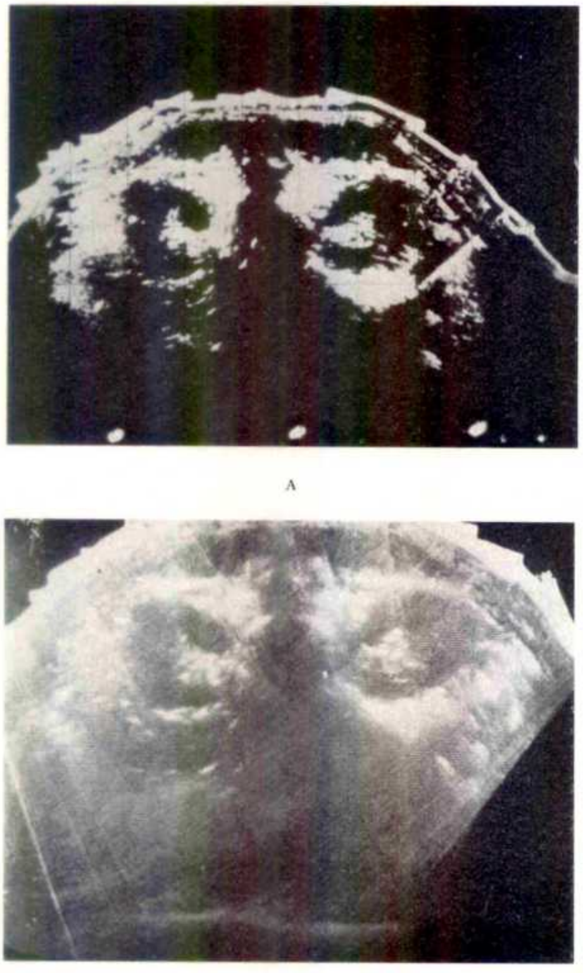
So far we have had three striking successes. Figure 1 illustrates the first of these in which a live baby resulted, though still badly affected and requiring two exchange transfusions after delivery. The placental characteristics changed notably after no less than 36 plasma exchange plasmaphereses of the mother's blood—no mean therapeutic undertaking. We still lacked however the facility which I will presently describe.

So far we have demonstrated our attempts at grey-scale representation using a conventional cathode ray tube with minimal persistence and open shutter photography with the scan carried out at a uniform high speed in order to avoid overloading the recording system (Donald, 1974) (Fig. 2). It must be admitted that the results so far are not good and this defect was accentuated by a further case in which the placenta was not only involved in Rhesus haemolytic disease but was praevia in situation as well. We lost the baby following two intra-uterine transfusions and the mother herself was in some peril from a major degree of placenta praevia.

Our frustration in patients with suspected malignant metastatic disease of the liver was equally great (Fig. 3). We tried every means that we could think of to try and eliminate artefacts and achieve meaningful resolution in the case of hepatic structure (Donald, 1973) but by now the need for a grey-scale technique was becoming increasingly obvious.

GREY-SCALE IMAGING

Up to this point, *i.e.* the autumn of 1974, we had to be content with echo information which only indifferently indicated the strength of the echo received and therefore the reflecting capacity of the structure under examination. For this we had to rely on brightness intensity modulation at each light dot on the face of the cathode ray tube which mapped the echo structure of a given tissue. This was achieved to some extent by varying the pulse width in accordance with echo strength but even with these refinements the pictures obtained, as can be seen, were made up in black or white without intermediate shades of grey tone such as one would see in an ordinary snapshot or on the face of a television set. Furthermore, storage tubes were used to an every increasing extent on most up-to-date machines



A

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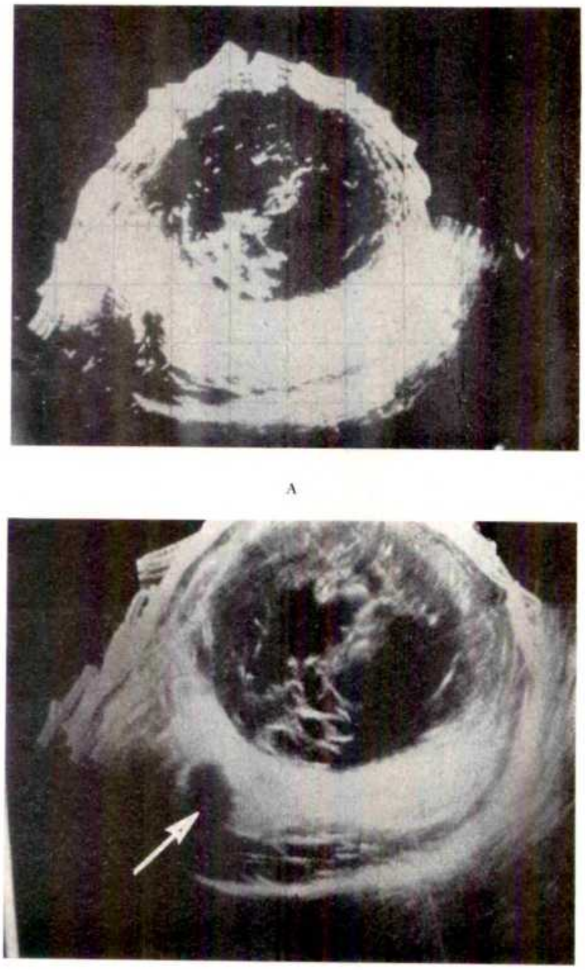
FIG. 9.

Transverse view of normal kidneys. Patient in prone position, (A) standard; (B) grey scale.



A

B

FIG. 10.

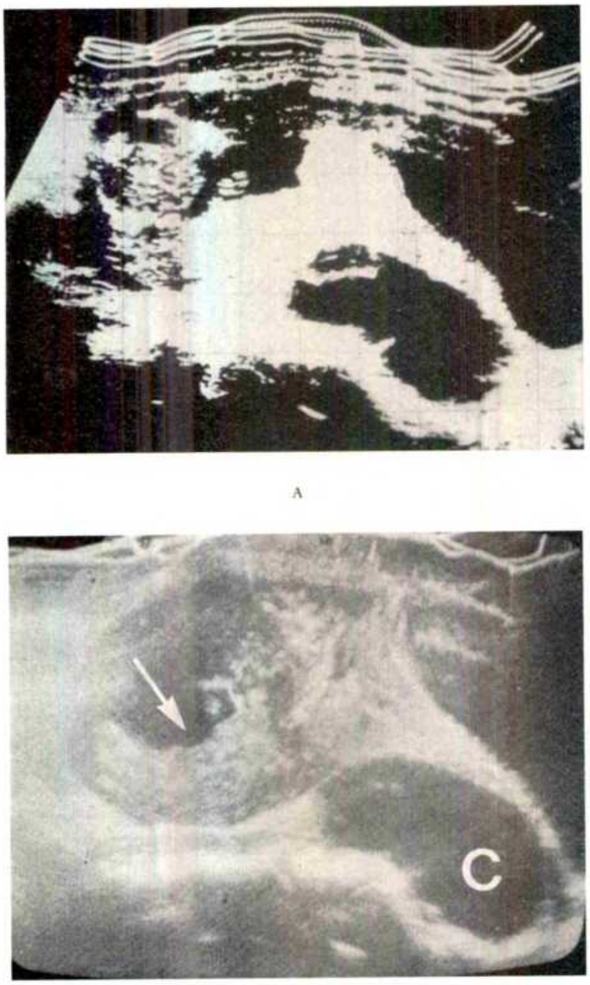
Large, secondary sarcomatous deposit in thigh, very haemorrhagic and lined with malignant tissue, (A) standard; (B) grey scale technique. Arrow indicates femur, which is not affected.

because one could simultaneously study the pictures obtained and photograph them there and then. But for all its great convenience storage inevitably resulted in some sacrifice of detail and resolution. Kossoff and his colleagues in Australia (Kossoff and Garrett, 1972; Kossoff *et al.*, 1973) have achieved some notably successful pictures in grey scale by meticulous attention to amplifier design and by employing film echography without intermediate storage. The use of water tanks also helped to improve the quality of their pictures.

Our department of Ultrasonic Technology has been very fortunate, in its unofficial but friendly association with the firm of Nuclear Enterprises Ltd., situated not so very far away in the Glaswegian suburb of Edinburgh. Together we have been able to work out, not for the first time, the feasibility in clinical practice of some new project. The latest among these is the scan converter, for the purpose of grey-scale imaging.

SCAN CONVERTER

Hitherto cathode ray tubes have operated by converting electrical signals into light signals on the screen which can be directly viewed, but now we have the Lithicon storage tube whose target is not a traditional phosphor but a mosaic of silicon and silicon oxide. This target material stores signals

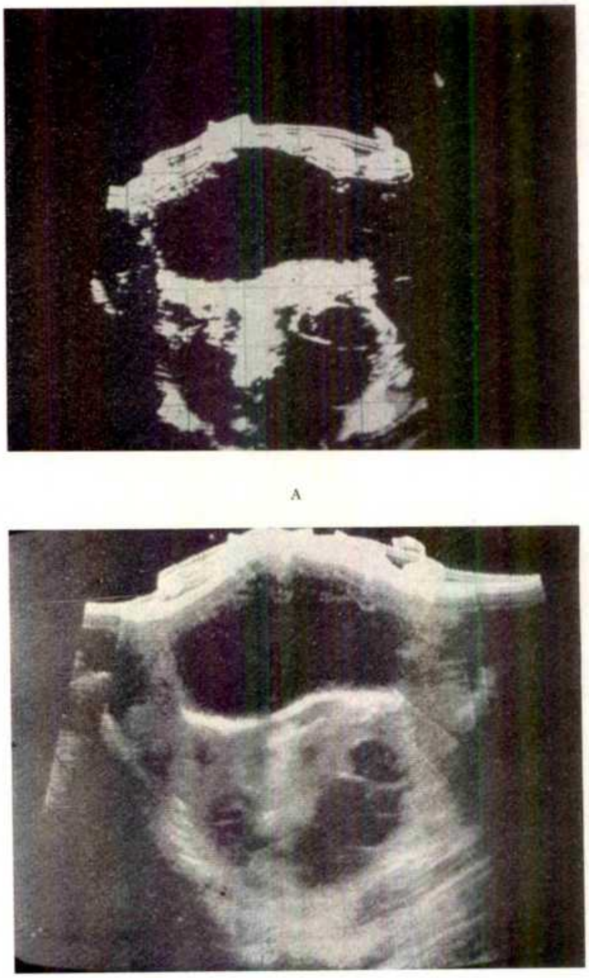


A

B

FIG. 11.

Large ovarian cyst impacted in pelvis below nineteen week pregnancy, (A) standard; (B) grey scale. Note low lying placenta in the uterus above the cyst. C.

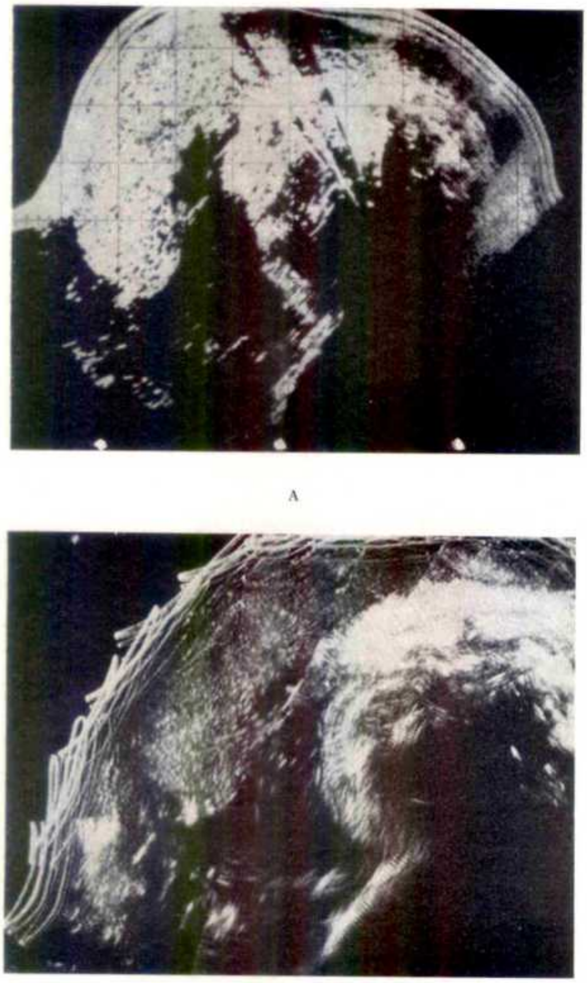


A

B

FIG. 12.

Bilateral tubo-ovarian abscesses in transverse section viewed through full bladder, (A) standard; (B) grey scale.

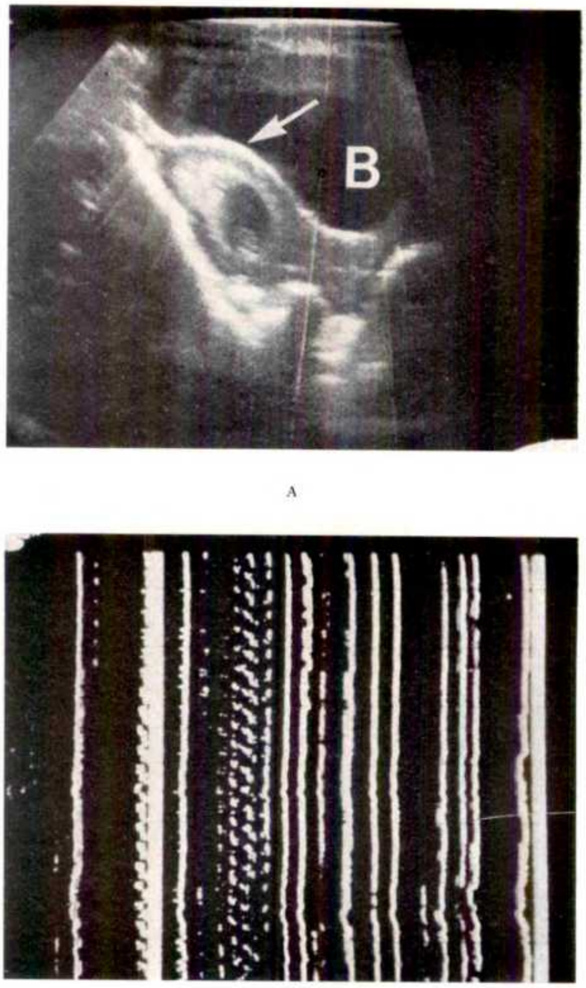


A

B

Fig. 13.

Transverse section of normal, antero lateral placenta at 33 weeks gestation, (A) standard; (B) grey scale.



A

B

Fig. 14.

Early pregnancy between eight and nine weeks menstrual age. Note fetus in the lower part of gestation sac and early beginnings of the placenta at the fundus (arrow) viewed through full bladder B in (A); (B) time-motion display of fetal cardiac activity obtained at the same examination. Width of this picture corresponds to 20 mm.

with a capacity for resolution greater than that of the electron beam striking it, which is now more likely to become the limiting factor; whereas storage was formerly achieved on a mesh situated immediately behind the light emitting phosphor screen. Such a mesh invariably limited resolution. This silicon storage target, which cannot be viewed, is raster scanned, as in television, by an electron gun and in conformity with this raster scan a signal can now be applied to a standard television tube in all its varying strengths producing at least ten shades of discernible grey. These scan conversion units were originally introduced for changing the American 525-line television system to the British 405 or 625 line system but clearly such a scheme can produce a raster display of say 625 lines from a random ultrasonic scan on a commercially available TV monitor.

Not only have we now a grey-scale capability but we also have, as already mentioned, very much greater resolution, and finally the target of a Lithicon cathode ray tube has a peak value memory. In other words it cannot, within limits be overloaded by overwriting since, from however many positions the subject is viewed, the highest value is stored

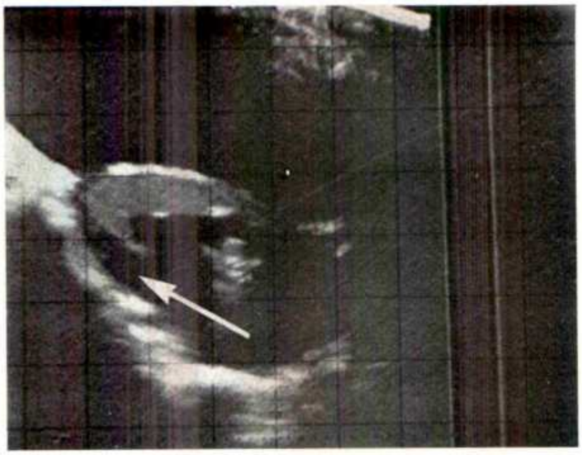
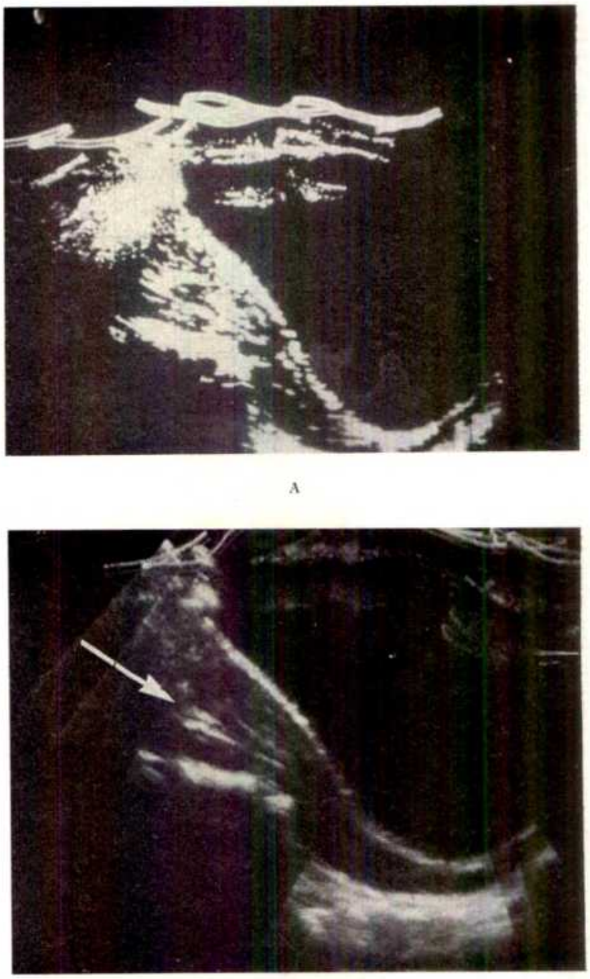


FIG. 15.

Erroneous clinical diagnosis of missed abortion on account of continued bleeding, negative urine tests, absent Doppler signals, 14 weeks amenorrhoea. This figure shows partially separated placenta near fundus and fetal body within the sac (arrow). Fetal heart also picked up by time-motion scanning. Active pregnancy of 12 weeks diagnosed and evacuation operation cancelled.



A

B

FIG. 16.

Secondary post-partum haemorrhage, two and a half weeks after normal spontaneous delivery, (A) standard; (B) grey scale. Note in (B) the separation of anterior and posterior walls of the uterus by a blood clot and strong echo near the top (arrow). At evacuation a small piece of placental tissue and bloodclot removed. Compared with (B), (A) is unintelligible.

and cannot thereafter be added to by further viewing. This enormously facilitates the task of ultrasonography in the hands of the inexperienced and requires appreciably less expertise.

COMPARISON OF STANDARD STORAGE AND SCAN CONVERTER STORAGE SYSTEMS

A simple diagram may explain this new technique as applied to sonar (Fig. 4). The next figure shows the effect of the technique in practice (Fig. 5). We are looking at the complex echoes presented by the fetal trunk in the case of a breech presentation. Along the bottom of the upper photograph (Fig. 5A) an A-scan trace with its variable heights of echo blip is superimposed upon an arrested line of B-mode dots as shown on the right. A cursor marker has been superimposed on each of these two traces. It will be observed that the variety of echo strength is very great as shown on A-scan and yet the amount of information obtainable from the B-scan is equally incomprehensible. The grey-scale picture below is a considerable improvement, showing the placenta and the various echoes from the fetal trunk, since it takes into account the great difference in reflecting properties of the structures encountered.

Once this technique became available we returned to the point some twenty years ago, to look again at gynaecological tumour masses and ascites (Figs. 6, 7). This led to our becoming involved in abdominal conditions which were not strictly gynaecological (Figs. 8, 9, 10). Meanwhile we continued to collect material in our own subject (Figs. 11, 12) and in particular to study the placenta adequately (Fig. 13). Soon, we returned to full bladder technique studies of very early pregnancy (Figs. 14, 15) (Donald, 1963). Other varieties of intra-uterine contents are likewise available for study (Figs. 16, 17).

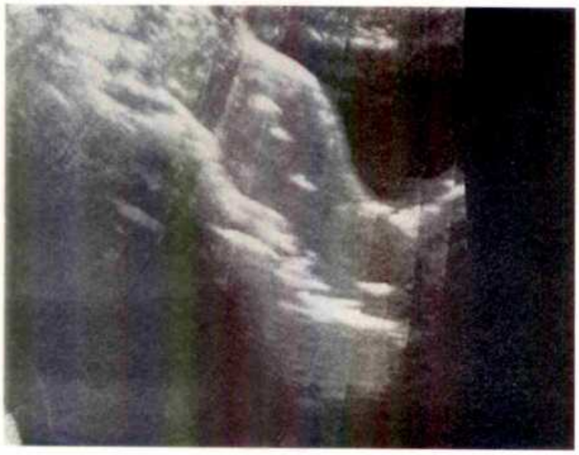


FIG. 17.
I.U.C.D. situated normally inside uterus. (The strings could not be found.)

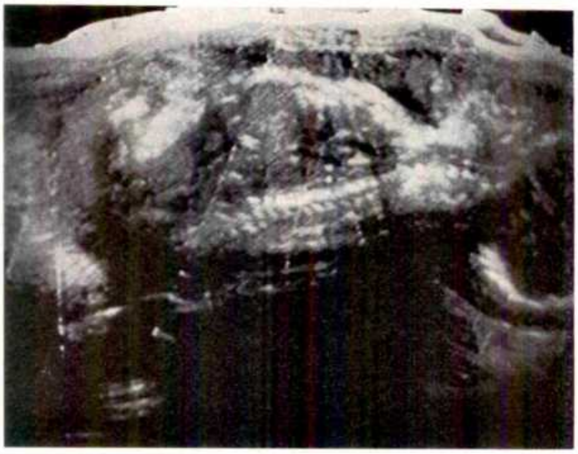


FIG. 19.
Normal, 32-week fetus in occipito-posterior position. Head engaged in pelvis. Note vertebral column and portions of ribs. Heart is visible, also interventricular septum. Note also diaphragm and liver.

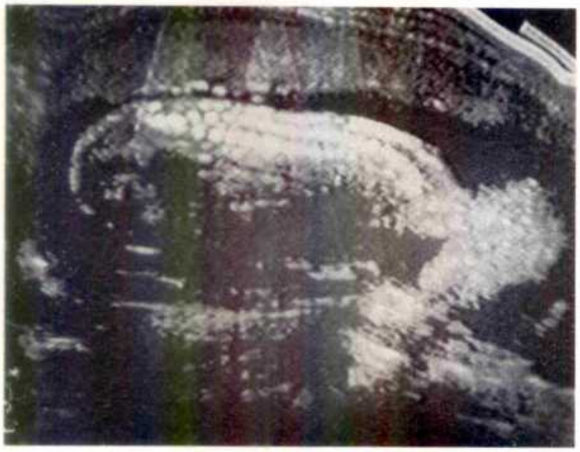


FIG. 18.
Fetal spine at 25 weeks. The cranial vault could not be included in this sectional view. Note upper anterior placenta.

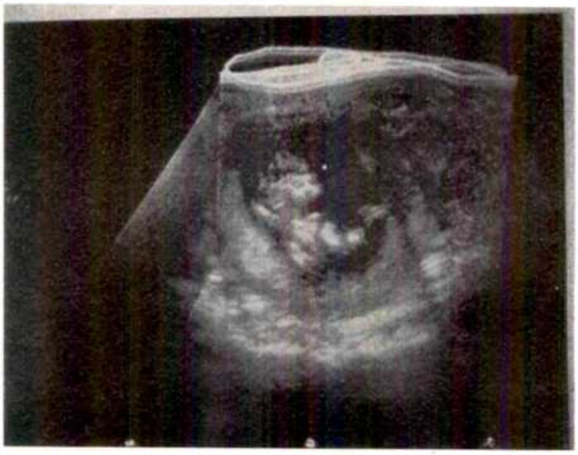


FIG. 20.
Normal 13-week pregnancy. It was not possible to include the lower part of trunk and legs in this view.

We began to wonder whether we might not be able to improve upon attempts by sonar to detect fetal abnormality *in utero* (Figs.18, 19). So far we lack experience but have always admired the work of Campbell *et al.* (1973) who, with existing apparatus, have demonstrated fetal bladder filling and emptying.

It can now be appreciated that our interest in very early fetal development and departures therefrom and in the blighted ovum (Donald *et al.*, 1972) has been enormously increased by this new facility. Three or four years ago, when working on the prototype NE4102 machine, we did well to produce a "view" of the fetus at seven weeks' gestation (menstrual age) and by this time we expect to be able to detect fetal heart movement in continuing pregnancy (Robinson, 1972). However, with the grey-scale facility of the new scan converter system we have done better still (Fig. 20).

I hope that I have demonstrated some of the capability of a new type of pictorial representation. The hurdle of grey scaling looks as though it is at last surmounted and, it should be noted, without sacrifice of anatomical detail. A fuzzy, out-of-focus picture is not a true grey-scale ultrasonogram. Linear clarity is just as important as ever before.

Instead of thinking of the beginning of the end I am reminded of Winston Churchill's phrase the "end of the beginning".

CONCLUSION

Sonar indeed employs a different energy spectrum from that of röntgenology and the information yield is consequently different but the whole ever-increasing science and art of existing visual diagnostic techniques can now embrace new horizons by adopting sonar not as a rival but as a complementary discipline. Whether the world of radiology likes it or not it will assuredly come to recognize and meet the challenge in the future.

ACKNOWLEDGMENTS

The apparatus taking the ultrasonograms illustrated is the standard NE4102 from Nuclear Enterprises Ltd., Edinburgh, and the grey-scale pictures have been produced with the same apparatus to which has been added the NE4104 scan converter unit. The combined research efforts of their engineers and our own ultrasonic research technologists, Mr. John Fleming and Mr. Angus Hall, have resulted in the rapid launching of this work. The medical personnel in this team, whom I am privileged to lead on a long-term research programme, include Dr. Hugh Robinson, Dr. Mary Pont and Dr. Judy Caines, who has recently returned to Canada. Their work and collaboration has made this presentation possible. I have also to acknowledge the great help with the illustrated material received from Mrs. Ida Miller and Mr. Ian McKie.

In addition to financial support directly from the University of Glasgow we have gratefully to acknowledge the long-term programme research grant awarded to me by the Medical Research Council and additional assistance from the Greater Glasgow Health Board. Finally, I would like to thank the best secretary in Scotland, Miss Adele Ure, and my gynaecological and radiological colleagues for their generous-hearted support and encouragement.

REFERENCES

BARNETT, E., and MORLEY, P., 1974. *Abdominal Echography*, ed. D. H. Trapnell (Butterworths, London).

BROWN, B., and GORDON, D. (Eds.), 1967. *Ultrasonic Techniques in Biology and Medicine* (Iliffe, London).

CAMPBELL, S., WLADIMIROFF, J. W., and DEWHURST, C. J., 1973. The antenatal measurement of fetal urine production. *Journal of Obstetrics and Gynaecology of the British Commonwealth, 80*, 680–686.

DONALD, I., 1963. The use of ultrasonics in the diagnosis of abdominal swellings. *British Medical Journal, 2*, 1154–1155.

1969. On launching a new diagnostic science. Joseph Price Oration. *American Journal of Obstetrics and Gynecology, 103*, 609–628.

1973. Ultrasonics in Medicine. Proceedings of 2nd World Congress on Ultrasonics in Medicine, Rotterdam. Eds. M. de Vlieger, D. N. White and V. R. McCready (Excerpta Medica, Amsterdam).

1974. New problems in sonar diagnosis. *American Journal of Obstretics and Gynecology, 118*, 299–309.

DONALD, I., and ABDULLA, U., 1968. Placentography by sonar. *Journal of Obstetrics and Gynaecology of the British Commonwealth, 75*, 993–1006.

DONALD, I., MACVICAR, J., and BROWN, T. G., 1958. Investigation of abdominal masses by pulsed ultrasound. *Lancet, 1*, 1188–1195.

DONALD, I., MORLEY, P., and BARNETT, E., 1972. The diagnosis of blighted ovum by sonar. *Journal of Obstetrics and Gynaecology of the British Commonwealth, 79*, 304–310.

KING, D. L. (Ed.), 1974. *Diagnostic Ultrasound* (Mosby, St. Louis).

KOSSOFF, G., and GARRETT, W. J., 1972. Ultrasonic film echography in gynecology and obstetrics. *Obstetrics and Gynecology, 40*, 299–305.

KOSSOFF, G., GARRETT, W. J., and RADOVANOVICK, G., 1973. *Grey Scale Echography in Obstetrics and Gynacology*. Commonwealth Acoustic Laboratories Report No. 59, Sydney, Australia.

LYONS, E. A., FLEMING, J. E. E., ARNEIL, G. C., MURPHY, A. W., SWEET, E. M., and DONALD, I., 1972. Nephrosonography in infants and children: A new technique. *British Medical Journal, 2*, 689–691.

ROBINSON, H. R., 1972. Detection of fetal heart movement in first trimester of pregnancy using pulsed ultrasound. *British Medical Journal, 4*, 466–468.

WELLS, P. N. T. (Ed.), 1972. *Ultrasonics in Clinical Diagnosis* (Churchill Livingstone, London).

1976, *British Journal of Radiology*, *49*, 316–320

A radiological study of morphology and growth in the human fetal colon

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(*Received September, 1975*)

ABSTRACT

A radiological study has been made of the colon in 64 human fetuses between 11 and 20 weeks gestation (64–160 mm crown rump (CR) length). A dynamic picture of colon development was obtained from analysis of the radiographs. The findings challenge textbook descriptions, but can be interpreted in terms of the ultimate morphology of the colon. According to the morphology of the proximal (pre-splenic) part of the colon, there are three types of colon. In Type 1 it lies transversely, in Type 2 it is oblique in direction, and Type 3 has a postnatal form with ascending and transverse elements. Although the Type 1 predominates in smaller fetuses and the type 3 is most common in larger fetuses, there is some overlap in their distribution. The ileocaecal junction does not descend, but actually slightly ascends as the fetus grows. The splenic flexure grows in a distinctly cranial direction, and at almost three times the rate of the ileocaecal junction. Thus, as the fetus develops, the ileocaecal junction and splenic flexure grow further apart, and this determines the change from a Type 1 to a Type 2 colon. The divergence of the ileocaecal junction and splenic flexure appears to be related to different rates of growth in the colon, the distal (post-splenic) part growing almost half as fast again as the proximal (pre-splenic) part. The more mature (Type 3) form of colon appears to result from conversion of the Type 2 following early adhesion between the proximal colon and the second part of the duodenum.

Previous studies of the development of the colon in the human fetus have been limited in several important respects. These include the examination of formalin-hardened tissues, opening of the abdominal cavity with displacement and manipulation of the intestine, examination of only small numbers of fetuses and limited or no statistical analysis of data (Frazer and Robins, 1916; Fitzgerald, Nolan and O'Neill, 1971).

The present study demonstrates how radiological material can be used to reconstruct dynamic aspects of prenatal growth and development. Detailed radiological examinations have been made of the developing colon in the human fetus between 11 and 20 weeks of age. The colon was examined radiologically in fresh fetuses less than 45 minutes after hysterotomy. By making accurate measurements on the unfixed and undisturbed colon within the intact abdomen a dynamic picture of prenatal colon development was constructed. The findings seriously challenge conventional descriptions of colon development as given in current embryology text-books (Hamilton and Mossman, 1972; Warwick and Williams, 1973).

MATERIALS AND METHODS

A total of 64 fetuses, between 11 and 20 weeks gestation (64–160 mm crown-rump (CR) length) was examined. Morphologically, each fetus appeared intact and without external abnormality. CR length was recorded with the head positioned in the Frankfurt plane. Radiography was performed within 45 minutes of delivery by hysterotomy. Small amounts of Conray 420 were slowly injected into the rectum via a small-bore plastic tube inserted per anum. Under careful radiological control the colon was filled retrogradely, small but repeated amounts of contrast medium being injected until the colon had been filled as far as the ileocaecal valve (Fig. 1). Complete filling was verified radiologically, and at the same time it was confirmed that the colon had not been distorted during the procedure. All radiographs were taken in the antero-posterior position with the fetus supine, the position being exactly reproducible so that subsequent measurements on other fetuses and their radiographs could be compared. The anode-film distance was 1·2 m with exposures of 45 to 50 kV at 230 mAs, using Kodirex non-screen film. After radiography, the abdomen was opened to confirm the position of the colon as originally shown on the radiographs.

The radiographs were examined from three aspects:

(1) general morphology of the colon;
(2) total length of the colon and its proximal (pre-splenic) and distal (post-splenic) parts;
(3) changes in position of the splenic flexure and the ileocaecal junction.

The proximal colon was defined as that part extending from the ileocaecal junction to the mid-point of the highest part of the splenic flexure, and the distal colon as extending from the splenic flexure

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A paper read at the Joint Radiological Meeting, Nottingham, September 27 and 28, 1974.

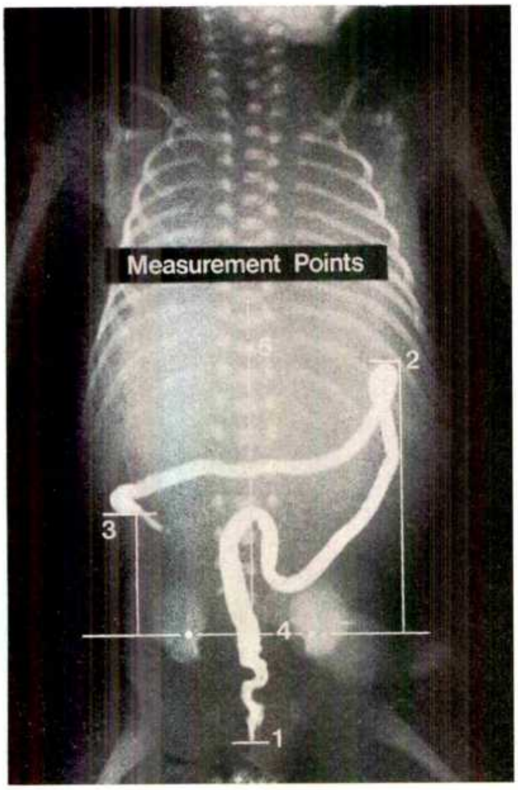

FIG. 1.

Definition of the measurement points. The distance between numbers 1, 2 and 3 represent the distal and proximal colon lengths respectively. Number 4 is the interosseous distance (IOD) on the interosseous plane (IOP). T10 vertebra is marked by 5.

to anal sphincter (Fig. 1). Using an overhead projector, the radiographs were projected onto white card, and the outline of the colon accurately traced. On the tracing, measurements were then made of the total colon length and of its proximal and distal segments using a map-measuring instrument with an accuracy of 0·5 mm. Projection of all the radiographs was made at a known fixed distance so that magnification was constant and easily calculated.

The positions of the ileocaecal junction and the splenic flexure were recorded in reference to a particular transverse plane (see Fig. 1)—the interosseous plane (IOP—a transverse line drawn between the points of maximum opacity in the ossifying hip-bone), and in reference to the mid-line vertical plane passing through the spinal column. The positions of the ileocaecal valve and splenic flexure were also noted in relation to the 10th thoracic vertebra.

It was hoped that morphological observations on the radiographs might show whether colon shape could be related to any particular stage of gestation. From the measurements of position and length it was hoped to construct a dynamic pattern of colon growth, including a comparison with general longitudinal somatic growth of the fetus.

STATISTICAL ANALYSIS

A computer program was used to determine single and multiple regression equations, analyses of variance, correlation coefficients and standard errors of the estimates.

RESULTS

Colon morphology

There appear to be three types of colon according to the morphology of the pre-splenic (proximal) part of the colon. In Type 1 the proximal colon is essentially transverse in position (Fig. 2A), in Type 2 it is oblique, passing from the lower right to the upper left quadrant of the abdomen (Fig. 2B), and in Type 3 it has ascending and transverse components (Fig. 2C). Although the transverse type predominates in the smaller fetuses, and the ascending/transverse type is most common in the larger fetuses, there is considerable overlap in the distribution of the three types (Fig. 3). Thus, a Type 1 colon is occasionally seen in a larger fetus and a Type 3 in a smaller fetus. Such variations are to be expected in biological material.

Colon length

The relationship between total length and maturity (using CR length as the index) is slightly curvilinear ($r=0{\cdot}95$), but the line of best fit is described by the linear regression equation, $y=-39{\cdot}66+1{\cdot}07x$ (Fig. 4). Figure 5 shows that the distal colon grows more rapidly, by a factor of 1·4, than the proximal colon and that both grow linearly with respect to fetal maturity.

The position of the ileocaecal junction and splenic flexure

As the fetus grows, both the ileocaecal junction and the splenic flexure migrate in a cranial direction when compared with the IOP. However, the proximal growth of the splenic flexure is considerably greater than that of the ileocaecal junction and is, in fact, comparable with vertical somatic growth using changes in the position of the 10th thoracic

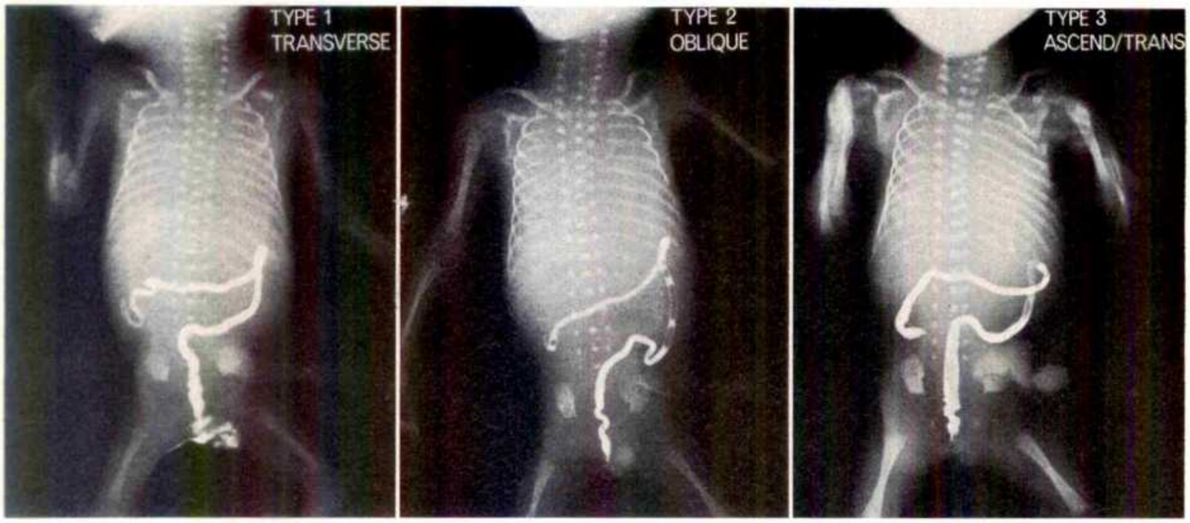

FIG. 2.
Types of colon morphology.
(A) Type 1, the proximal colon is essentially transverse.
(B) Type 2, oblique.
(C) Type 3, the proximal (pre-splenic) colon showing ascending and transverse components.

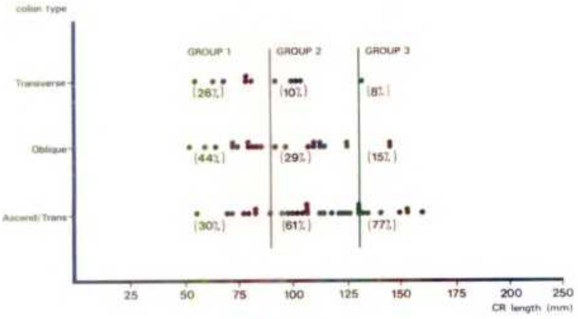

FIG. 3.
Distribution of colon types according to gestation.

vertebra as the index (Fig. 6). Due to the differences in growth rates of the pre-splenic (proximal) and post-splenic (distal) colon, the vertical movement of the splenic flexure is approximately three times that of the ileocaecal junction, the latter lagging behind the vertical movement of the splenic flexure. In addition to their vertical growth, the ileocaecal junction and splenic flexure grow laterally, away from the mid-line (Fig. 7).

DISCUSSION

A conventional description of colon development is given by Hamilton and Mossman (1972). The physiological "herniation" of the primary intestinal loop into the extra-embryonic coelom occurs

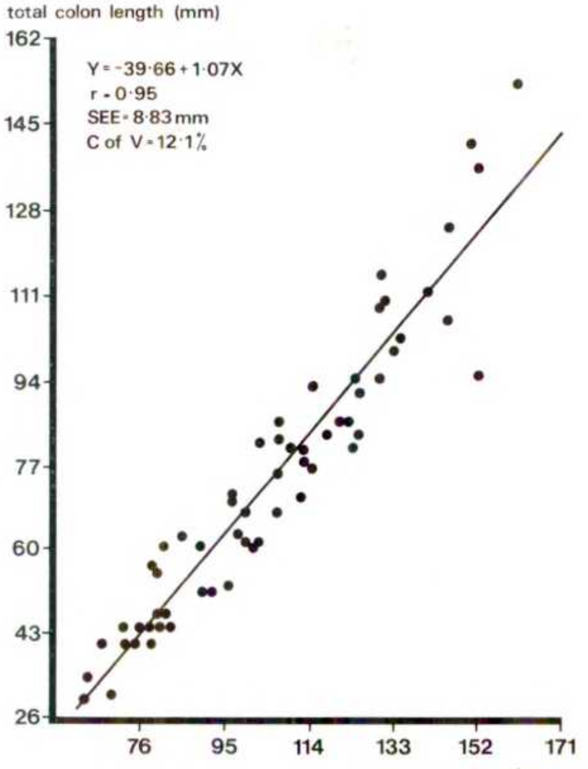

FIG. 4.
The relationship of human fetal total colon length to crown-rump length.

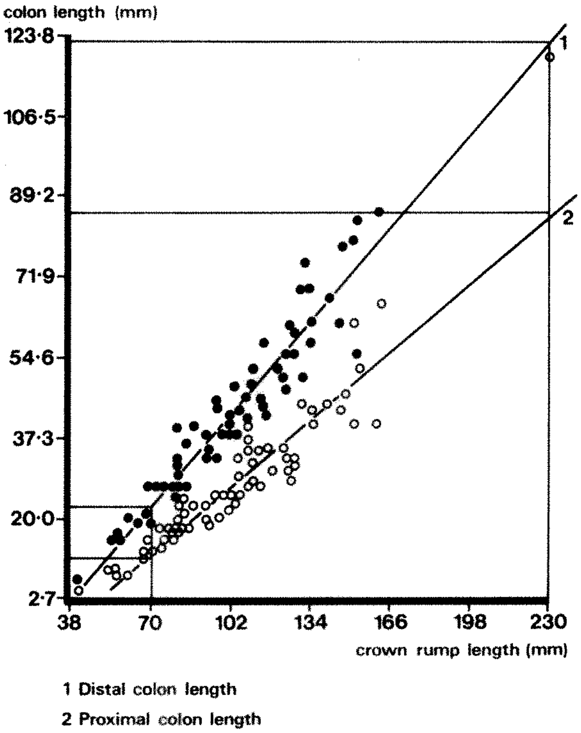

Fig. 5.

Growth differences in the proximal (pre-splenic) and distal (post-splenic) colon are demonstrated when individually regressed on crown-rump length.

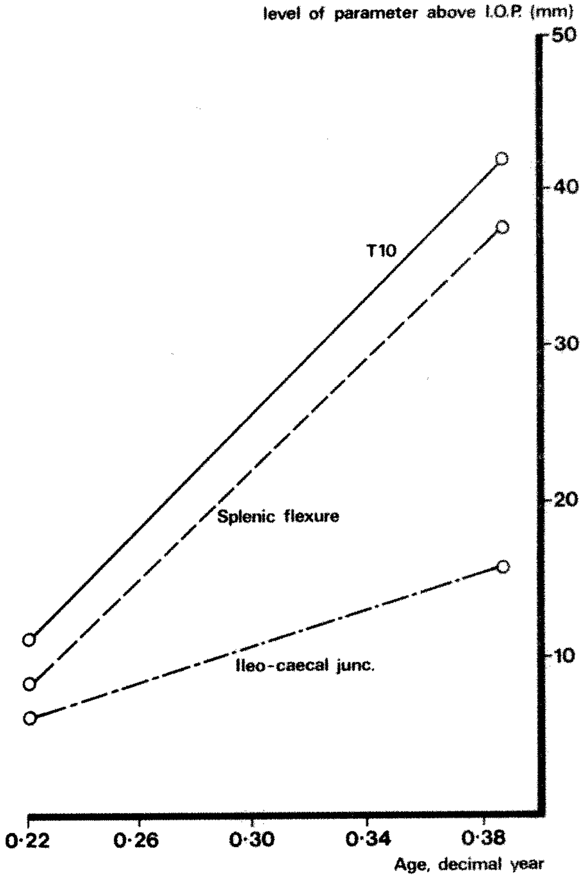

Fig. 6.

Growth differences in the 10th thoracic vertebra, splenic flexure and ileocaecal junction in relation to fetal age.

during the sixth week and it returns through the body stalk during the 12th week. The last part to reduce is said to be the caecum which comes to lie in the upper right quadrant of the abdomen beneath the right lobe of the liver. With further growth the caecum is described as progressively *descending* until it eventually reaches its typical post-natal position in the right iliac fossa.

The important advantages of the present study over those of previous workers are that it was made on unfixed, near-viable material (within 45 minutes of hysterotomy) and there was no disturbance of abdominal contents or displacement of organs which almost inevitably accompany opening of the abdomen.

The conventional account of colon development is at variance with the present findings since it implies greater growth in the pre- rather than in the post-splenic part of the colon, whereas the findings in the present study are exactly the opposite. It is of interest that the distal colon corresponds to the hind-gut section of the primitive gut tube, while the pre-splenic or proximal part corresponds to part of the primitive mid-gut. Moreover, each part has its own separate blood supply. It is this difference in growth rate which causes the ileocaecal junction to lag appreciably behind the vertical growth of the splenic flexure in a cranial direction. Thus, as the fetus matures the splenic flexure and ileocaecal junction become increasingly further apart, not only in a vertical plane but also in a transverse direction. This explains the change from a Type 1, transverse morphology of the pre-splenic colon to the transitional oblique form of the Type 2. What determines, with further growth, the development of the Type 3 colon? This type resembles the mature post-natal colon having both ascending and transverse elements. It appears to result from early adherence between the future transverse colon and what is destined to become the second part of the duodenum

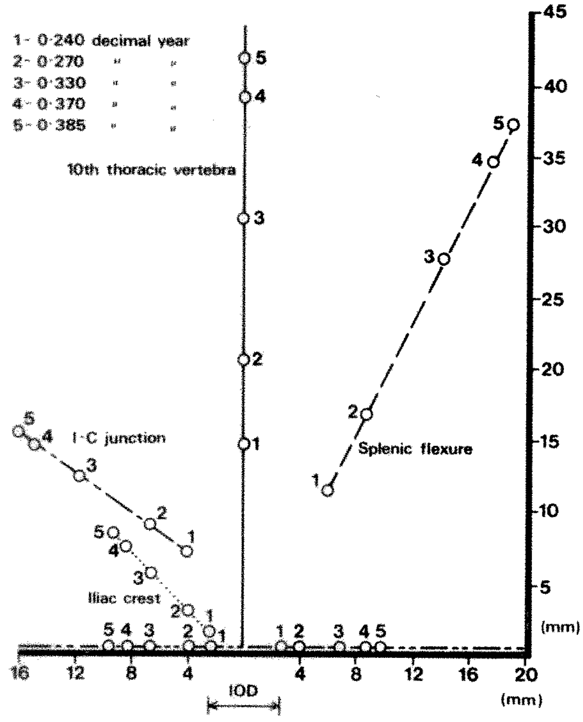

Fig. 7.

Comparative movement of the measurement points.

(Hamilton and Mossman, 1972). Were it not for this adhesion, the Type 2, oblique form of colon would persist.

The conventional description of a marked *downward* growth of the caecum into the right iliac fossa is not supported by the present studies. In fact, we suggest the opposite happens, that is, there is some ascent in reference to the IOP although, because of the expansion of ossification in the iliac bones, the position of the ileocaecal junction appears to remain constant in relation to pelvic bones.

The reason for the more rapid growth of the post-splenic part of the colon is obscure. Several factors may contribute. There may be traction on the splenic flexure by the phrenico-colic ligament which binds it to the diaphragm which is itself involved in somatic growth as the abdominal cavity enlarges. It may be related to the time of absorption of mesenteries, that of the descending colon disappearing first so that the colon becomes less mobile and splinted to the posterior abdominal wall, there to be influenced by the rate of growth of the abdominal wall. Finally, it is intriguing to note that the post-splenic colon has a different blood supply (inferior mesenteric artery) when compared with that of the pre-splenic segment (superior mesenteric artery).

Acknowledgments

The authors are indebted to Professor R. E. Coupland, Department of Human Morphology, Nottingham University Medical School, who kindly made available the fetuses for this study; also to Dr. E. J. Roebuck, consultant radiologist, the Misses M. Beake and M. Lee, radiographers, Nottingham General Hospital, who provided and carried out the radiological services respectively. Our appreciation is also due to Miss Pat Bloodsworth, Audio Visual Aids Unit, University of Technology, Loughborough, for the graphic design.

REFERENCES

Fitzgerald, M. J. T., Nolan, J. P., and O'Neill, M. N., 1971. The position of the human caecum in fetal life. *Journal of Anatomy*, *109*, 71–74.

Frazer, J. E., and Robins, R. H., 1916. On the factors concerned in causing rotation of the intestine in man. *Journal of Anatomy and Physiology*, *50*, 75–110.

Hamilton, W. J., and Mossman, H. W., 1972. In *Human embryology*, 4th edn. (W. Heffer & Sons Ltd., Cambridge).

Warwick, R., and Williams, P. L., 1973. In *Gray's Anatomy*, 35th edn., pp. 172–174 (Longman, Edinburgh).

1976, *British Journal of Radiology*, *49*, 321–325

Nephrographic density and renal diatrizoate content in experimental acute renal failure

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(*Received October, 1975*)

Abstract

Reversible acute renal failure (ARF) was induced in rats by intramuscular injection of glycerol. In these animals and controls, renal concentrations of ^{125}I-labelled sodium diatrizoate, injected intravenously in doses similar to those used clinically, were compared with the density of the nephrogram, subjectively assessed under carefully controlled conditions. Though a good statistical correlation existed between renal diatrizoate concentration and nephrographic density, individual variation was wide. At any given level of renal iodine concentration, nephrograms were judged to be denser in ARF than in controls. This was not due to differences in whole-body opacification or renal size, but was partly explained by the greater visibility of renal outlines on plain films in ARF. However, though at all doses of diatrizoate renal iodine concentrations were higher in controls, differences in nephrographic density were in general difficult to detect.

Reversible acute renal failure (ARF), frequently called acute tubular necrosis, is characterized in most cases by severely depressed urine output. This appears to result from reduction in glomerular filtration (Oken *et al.*, 1966). Since diatrizoate, at doses used for intravenous urography, is excreted almost entirely by this route (Denneberg, 1965; Cattell *et al.*, 1967; Donaldson, 1968), the appearance of nephrograms of normal density during intravenous urography in ARF (Cattell *et al.*, 1973; Sherwood *et al.*, 1974) is difficult to explain. The lesion induced in the rat kidney by the intramuscular injection of glycerol resembles clinical ARF (Finckh, 1957; Oken *et al.*, 1966; Munck, 1975). Previous measurements of renal diatrizoate concentration in this experimental model recorded values which, over a wide range of doses, were much lower than those in the kidneys of control animals (McLachlan *et al.*, 1974; Robinson *et al.*, 1976). The present work compares visual assessments of nephrographic density in control rats and those in glycerol-induced ARF, and relates these assessments to renal concentrations of diatrizoate.

Methods

After weighing, 101 Wistar rats (mean weight 198 g, range 180–220 g) were placed in individual metabolic cages, which allowed collection of urine uncontaminated by faeces, food or drinking-water. ARF was induced in 50 rats by the intramuscular injection of 10 ml./kg bodyweight of 50 per cent glycerol after overnight (12 hours) dehydration. Except for this period, all animals were allowed free access to tap water and Oxoid diet 41B. After 48 hours, the animals were anaesthetized by intraperitoneal injection of chloral hydrate (150–300 mg/kg bodyweight). The renal areas were radiographed using half of a rapid-processing film (Kodak RP 54), the other half being protected by lead. The same high-speed screen cassette (Dupont Cronex Hi-plus) was used for every animal. ^{125}I-labelled sodium diatrizoate was injected intravenously over ten seconds. The renal areas were again radiographed, using the unexposed half of the film, 60 seconds after the start of the diatrizoate injection and within three minutes of the control exposure. The same factors were used for all exposures: 100 mA, 0·02 seconds, 48 kVp at 100 cm tube-film distance. Focal spot size was 1·2 mm. Films were automatically processed using a 90-second cycle. Immediately after the second exposure, the abdomen was opened and both pedicles were clamped. The kidneys were removed intact. The lower pole of the spleen was also removed and blood collected from the inferior vena cava. Tissue and plasma samples were weighed in capped tubes.

Labelled diatrizoate was diluted with non-radioactive sodium diatrizoate. Each animal received a dose of 135, 270, 540 or 1,080 mg iodine/kg bodyweight in a volume of 1 ml.; equal to 0·05, 1, 2, or 4 ml./kg of 45 per cent sodium diatrizoate. The injected dose was measured by counting the radioactivity of syringes before and after injection using a portable scintillation counter. The observed counts were corrected for self-absorption of radiation. The activity of plasma and tissue samples was measured on an automatic gamma-counter. Results, except where otherwise stated, are expressed as mg iodine per gram of tissue or plasma. Renal values represent the mean of results for both kidneys. Plasma urea and creatinine were measured by a modified Technicon method.

Nephrograms were assessed by two radiologists

(P.J.A.R. and M.S.F.M.) independently on two separate occasions by comparing exposures obtained before and after diatrizoate injection. Radiographs were examined in random order with identifying marks concealed. An arbitrary scale from 0 (no visible nephrogram) to 3 (dense nephrogram) was used. The total nephrographic score for each animal was the sum of four assessments giving a range of 0–12. The number of renal outlines visible before injection of diatrizoate was noted independently on two occasions by both radiologists, who then agreed on their final conclusions.

Results

Table I shows numbers of animals and doses of diatrizoate used. Plasma urea and creatinine values and urine volumes and osmolalities are shown in Table II.

Figure 1 shows plasma and renal iodine concentrations. In control animals and those in ARF, the increase in plasma iodine values with dose is linear. This is also true of renal iodine concentrations in ARF. In controls, the increase in renal concentrations becomes less at the highest doses. Mean diatrizoate concentrations in the spleen, expressed as per cent injected dose per gram of tissue, was 0·49 (SD 0·36) in controls and 0·48 (SD 0·33) in animals in ARF.

None of the four individual scores for the nephrogram in each animal differed by more than one point. Differences were evenly distributed among groups. The effect of dose on nephrographic score is shown in Fig. 2. In ARF, these scores increase with dose in a linear manner. A greater rate of increase is seen in control animals with doses up to 540 mg iodine/kg bodyweight; at higher doses a much smaller increase occurs. The difference in nephrographic scores between ARF animals and controls is most marked at 540 mg iodine/kg.

Figure 3 compares renal iodine concentrations and nephrographic scores. Although correlation is good ($r=0{\cdot}81$, $n=101$, $p<0{\cdot}001$), wide individual variation exists. Correlation between scores and renal concentrations in ARF ($r=0{\cdot}83$) and in controls ($r=0{\cdot}81$) was similar. Figure 3 also shows that, in general, animals with ARF received higher nephrographic scores than controls with similar renal iodine concentrations. These differences are shown in Fig. 4, in which nephrographic scores are grouped. In animals in ARF, 28 of 100 renal outlines were

TABLE I

Numbers of animals in each group

	Dose of diatrizoate as mg iodine/kg bodyweight				
	135	270	540	1080	Totals
Controls	12	13	13	13	51
ARF	12	13	12	13	50
Totals	24	26	25	26	101

TABLE II

	Plasma urea (mmol./l.)	Plasma creatinine (μmol./l.)	Urine volume (ml./48hr)	Urine osmolality (mOsm/kg
Controls				
Mean	8·4	49·2	19·0	1554·0
SD	1·7	5·4	11·0	671·0
Range	6·3–15·0	40·0–60·0	2·0–53·5	768·0–2933·0
ARF				
Mean	93·7	683·7	8·0	682·0
SD	16·3	120·6	10·5	280·0
Range	36·0–122·0	170·0–1026·0	0–42·0	322·0–1766·0

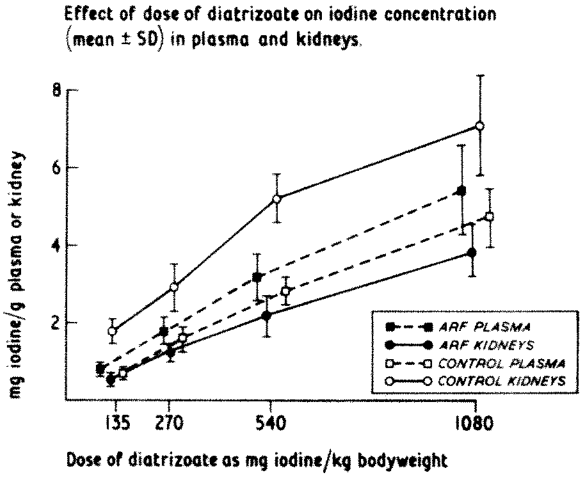

Fig. 1.

Renal and plasma concentrations of iodine compared with intravenous doses of diatrizoate in rats in acute renal failure (ARF) and controls. In ARF, the increase in renal iodine concentration with dose is linear. In controls, which at all doses have higher renal iodine concentrations, this increase diminishes at the highest doses, due to the diuretic effect of diatrizoate. Early excretion in controls leads to slight differences in plasma values between the two groups. Doses range from 0·5–4 ml. per kg bodyweight of 45 per cent sodium diatrizoate.

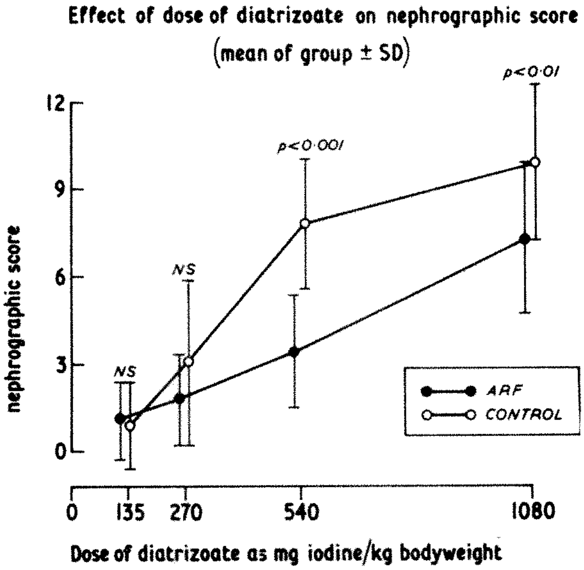

Fig. 2.

Nephrographic density, scored on a scale 0–12, compared with dose of diatrizoate. In general, scores follow the same trend as renal iodine concentrations but separation between the two groups is much less distinct. Levels of significance of differences are indicated. (NS = not significant).

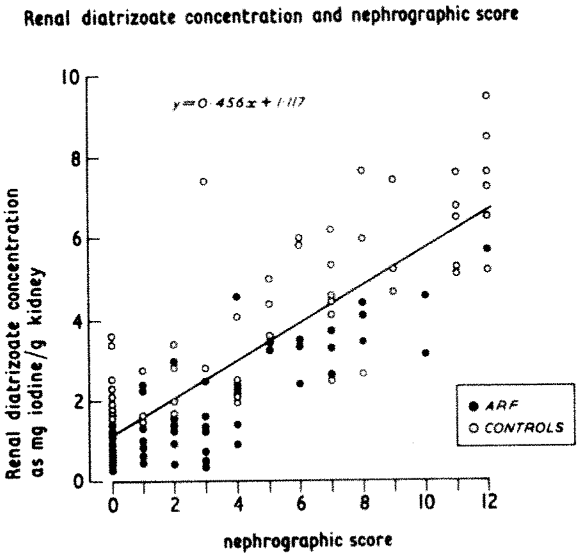

Fig. 3.

Nephrographic scores compared with renal diatrizoate concentrations. Correlation is good ($r=0{\cdot}81$, $p<0{\cdot}001$) but individual variation is wide; at renal iodine concentrations of 1·5–4 mg/g, scores range from 0 to 10. Assessment of nephrographic density tends to overestimate renal iodine concentration in ARF *vis-à-vis* controls (see also Fig. 4), but scores in ARF are generally lower than in controls.

visible on plain films; in controls 17 of 102 were visible ($p<0{\cdot}05$, $\chi^2=4{\cdot}96$). Renal iodine concentrations and nephrographic scores in ARF were not significantly correlated with plasma urea or creatinine values or with urine volumes or osmolalities.

Discussion

Nephrographic density is difficult to quantify (Doyle *et al.*, 1967; Fry and Cattell, 1972, Sherwood *et al.*, 1974). In the present study, nephrograms were assessed by comparing two radiographic exposures obtained side by side on the same film immediately before and after intravenous injection of diatrizoate. In this way, we were able to minimize the effects of variations in radiographic density not resulting from injection of contrast medium. Observer variation and bias were reduced by multiple assessments in each animal without knowledge of the group to which it belonged. Under these carefully controlled conditions, we confirmed the statistical relationship between nephrographic density and renal iodine concentration assumed by others (Doyle *et al.*, 1967; Cattell *et al.*, 1967; Saxton, 1969; Fry and Cattell, 1972). In patients, in whom the conditions obtaining in this study would be difficult to reproduce, the relationship is unlikely to be so close. Even in the present conditions, visual assessment of nephrographic density as an index of renal content of contrast medium may mislead. For example, four separate assessments revealed no visible nephrogram in nine control animals in which renal

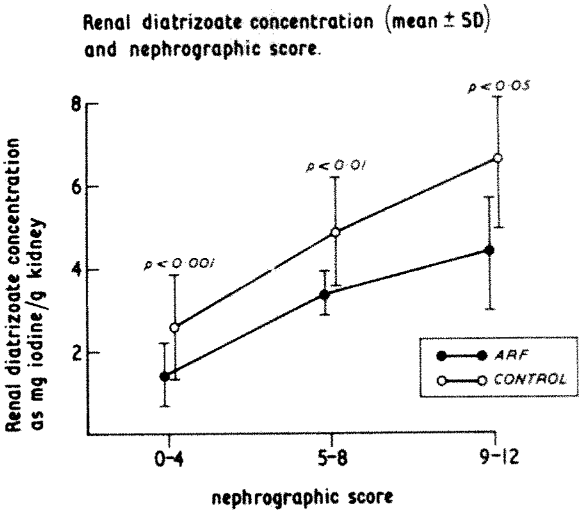

Fig. 4.

Grouped nephrographic scores compared with renal diatrizoate concentrations. At each level of nephrographic density, diatrizoate concentrations are significantly higher in controls.

iodine concentrations resembled those observed in 12 other animals showing nephrograms of intermediate or high density with nephrographic scores of 5 or more.

At all levels of renal iodine concentration, we judged nephrographic density to be greater in ARF. This is not explained by differences in whole-body opacification, as indicated by diatrizoate concentrations in plasma or spleen. Contrast medium in the renal pelvis could influence renal iodine concentration without contributing to nephrographic density. However, the difference in density between the two groups was not reduced by excluding six rats showing pyelograms, all being control animals given the highest dose of diatrizoate. Furthermore previous work in the rat (McLachlan *et al.*, 1974) showed no reduction in renal diatrizoate concentration when kidneys were sliced, opening the collecting system. Visual assessment of the density of faint opacities is closely linked to the sharpness of their edge (Newell and Garneau, 1951; Tuddenham, 1957). Our tendency to give higher nephrographic scores to animals in ARF may have been due to the greater readiness with which we could see their renal outlines, even before injection of contrast medium. Marked edge-enhancement during intravenous urography in ARF in the rat, with dense opacification of an outer rim of renal tissue (McLachlan *et al.*, 1972), is unusual and occurred once in the present series. Though similar appearances are reported in severely ischaemic human kidneys (Frank *et al.*, 1974) we have no evidence to suggest that this degree of reinforcement of renal outlines contributes to assessments of nephrographic density in ARF in man. The 30 per cent increase in renal weight which occurs in ARF in the rat and in man (Bohle *et al.*, 1960, McLachlan *et al.*, 1974) cannot explain these differences in nephrographic density. They persist when results are expressed as whole kidney content, *i.e.* mg iodine per kidney rather than concentration. Furthermore, in kidneys with equal content, rather than equal concentration, it might be expected that smaller kidneys would appear denser; we observed the converse.

Previous observations (Robinson *et al.*, 1976) showed that in this model of ARF in the rat renal concentrations of diatrizoate increase with dose in a linear manner; in control animals this increase is limited by the diuretic effect of large doses. As a result, although renal iodine concentration is higher in control animals at all doses, these differences diminish as dosage is increased. The present study which, like the previous one, employed doses resembling those in clinical use, indicates that the relationship between dose and nephrographic density is similar. However, differences in nephrographic density between the two groups are much less distinct, considerable overlap occurring at doses higher or lower than 2 ml./kg bodyweight of 45 per cent sodium diatrizoate. At each dose, nephrographic scores in ARF closely resemble those in control animals given half as much contrast medium. Notwithstanding species differences, our results suggest that the early nephrogram in patients in ARF receiving approximately 600 mg iodine per kg bodyweight (Cattell *et al.*, 1973; Sherwood *et al.*, 1974) can be expected to be similar in density to that observed in normal subjects given only half this dose.

ACKNOWLEDGMENTS

Financial support was received from Kodak Ltd., Ilford Ltd., and the Yorkshire Regional Health Authority. The X-ray equipment used was purchased with the help of a grant from the Medical Research Council. Schering Chemicals Ltd. supplied labelled diatrizoate. Dr. T. Davies and the Department of Medicine at the General Infirmary, Leeds, provided γ-counting facilities. Dr. D. B. Morgan and the Department of Chemical Pathology, University of Leeds, measured plasma urea and creatinine.

REFERENCES

Bohle, A., Herfarth, C., and Krecke, M. H., 1960. Beitrag zur Morphologie der Niere beim akuten Nierenversagen. *Klinische Wochenschrift, 38*, 152–164.

Cattell, W. R., Fry, I. K., Spencer, A. G., and Purkiss, P., 1967. Excretion urography. I. Factors determining the excretion of hypaque. *British Journal of Radiology, 40*, 561–571.

Cattell, W. R., McIntosh, C. S., Moseley, I. F., and Fry, I. K., 1973. Excretion urography in acute renal failure. *British Medical Journal, 2*, 575–578.

Denneberg, T., 1965. Clinical studies on kidney function with radioactive sodium diatrizoate (Hypaque). *Acta Medica Scandinavica, Suppl. 442*, 1–34.

Donaldson, I. M. L., 1968. Comparison of the renal clearances of inulin and radioactive diatrizoate (Hypaque) as measures of the glomerular filtration rate in man. *Clinical Science, 35*, 513–524.

Doyle, F. H., Sherwood, T., Steiner, R. E., Breckenridge, A., and Dollery, C. T., 1967. Large dose urography. Is there an optimum dose? *Lancet, 2*, 964–966.

Finckh, E. S., 1957. Experimental acute tubular nephrosis following subcutaneous injection of glycerol. *Journal of Pathology and Bacteriology, 73*, 69–85.

Frank, P. H., Nuttall, J., Brander, W. L., and Prosser, D., 1974. The cortical rim sign of renal infarction. *British Journal of Radiology, 47*, 875–878.

Fry, I. K., and Cattell, W. R., 1972. The nephrographic pattern during excretion urography. *British Medical Bulletin, 28*, 227–232.

McLachlan, M. S. F., Chick, S., Roberts, E. E., and Asscher, A. W., 1972. Intravenous urography in experimental acute renal failure in the rat. *Investigative Radiology, 7*, 466–473.

McLachlan, M. S. F., Davies, R. L., and Leach, K. G., 1974. Diatrizoate levels in the kidney and lymph nodes in acute renal failure in the rat. *Nephron, 13*, 443–454.

Munck, O., 1975. The physiology of acute renal failure. *British Journal of Radiology, 48*, 768–769.

Newell, R. R., and Garneau, R., 1951. The threshold visibility of pulmonary shadows. *Radiology, 56*, 409–415.

Oken, D. E., Arce, M. L., and Wilson, D. R., 1966. Glycerol induced hemoglobinuric acute renal failure in the rat. I. Micropuncture study of the development of oliguria. *Journal of Clinical Investigation*, *45*, 724–735.

ROBINSON, P. J. A., GAUNT, A., and MCLACHLAN, M. S. F., 1976. Effect of dose on renal diatrizoate concentrations in experimental acute renal failure. *Nephron* (in press).

SAXTON, H. M., 1969. Urography. *British Journal of Radiology*, *42*, 321–346.

SHERWOOD, T., DOYLE, F. H., BOULTON-JONES, M., JOEKES, A. M., PETERS, D. K., and SISSONS, P., 1974. The intravenous urogram in acute renal failure. *British Journal of Radiology*, *47*, 368–372.

TUDDENHAM, W. J., 1957. The visual physiology of roentgen diagnosis. *American Journal of Roentgenology*, *78*, 116–123.

Book review

Cardiac Catheterization and Angiocardiography in Severe Neonatal Heart Disease. By Michael T. Gyepes and William R. Vincent, pp. xi+184, 1974 (Springfield, Illinois, U.S.A., Chas. C. Thomas), $14.50.

Although there has been a great advance in the investigation of congenital cardiac disease in recent years, the neonatal period remains one of the most difficult areas for decision and action. Errors in diagnosis are not infrequent and may be final.

An informed team approach to such problems is very important in achieving early diagnosis and rapid action and, although nothing can replace practical experience, a great deal can be learnt from the expertise of others, provided that information is presented with sufficient clarity.

The book is written "primarily for trainees in paediatric cardiology and paediatric cardiovascular radiology". The authors, a paediatric radiologist and a paediatric cardiologist, address themselves to the problem of emergency diagnosis in severe neonatal heart disease and maintain that without early, swift and accurate diagnosis in this age group optimal patient salvage cannot be achieved. The book is divided into three sections headed simply Before, During and After. Hence Part I deals with the investigating which must precede cardiac catheterization. Part II discusses the details of cardiac catheterization, angiocardiography and equipment including a brief but adequate section called "When to Stop" and finally Part III relates to management once all the necessary information has been obtained.

The work is clearly based on considerable personal experience and strikes a balanced approach which those "immersed" in this particular field will applaud without reservation. It is perhaps surprising that so little attention is paid in the text to haemodynamic findings in the various conditions described; possibly it was felt that too much detail would detract from the overall value and blur the message. Throughout the work the clarity of description, the emphasis on especially telling diagnostic points and the informed dogmatic statements where these are most relevant all speak to the depth of practical knowledge and clinical grasp of the authors.

It is perhaps a little odd that a book with this team approach to neonatal heart disease has not been published before because the method advocated is surely the one practised in most paediatric cardiology centres of repute. Although this is the best work of its kind so far available in this country it is of little value to the general radiologist or those working for a diploma in diagnostic radiology. It is a specialist book for the aspiring specialist and in this capacity it is highly recommended.

B. STRICKLAND.

1976, *British Journal of Radiology*, *49*, 326–329

The diagnostic value of sialography and scintigraphy in salivary gland diseases

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(Received July, 1975 and in revised form November, 1975)

ABSTRACT

The diagnostic value of sialographic and scintigraphic investigations was compared in 169 patients.

In this group were 75 inflammatory diseases and 49 benign and malignant tumours.

Sialograms and scintigrams were examined by different physicians who had no knowledge of the clinical data of the patients.

The scintigraphic diagnosis was considered correct if any abnormal finding was noted. The sialographic diagnosis was considered correct if the actual disease was diagnosed.

In spite of the less stringent requirements for a correct scintigraphic diagnosis the sialographic technique was found to be superior. Radioactivity uptake curves over the salivary glands did not improve the scintigraphic diagnostic accuracy.

Sialography is the usual atraumatic radiological method for the evaluation of salivary gland disorders (White, 1974). Technetium scanning of salivary glands, introduced by Börner, has been recommended as a simple method with reasonable diagnostic accuracy (Börner *et al.*, 1965; Gates, 1972).

The following study was designed to examine the diagnostic value of each of the two methods using an independent interpretation of scans and radiographs of various abnormalities of salivary glands.

METHODS

Sialography

Water soluble contrast medium (0·5–2·0 ml. Urografin®, iodine content 370 mg ml.$^{-1}$) was used in about 50 patients with suspected obstruction of the major duct. Oily contrast medium (0·5–1·5 ml. Lipiodol®, iodine content 480 mg ml.$^{-1}$) was used in the remaining cases.

Serial spot films were obtained under fluoroscopic control during the injection of the contrast medium, during parenchymal opacification and after evacuation. Spot films were exposed at 105 kV to reduce the contrast of superimposed bone structures.

Technetium scanning

One mCi of ^{99}Tc^{m}O$_4$ was injected intravenously. Immediately prior to the administration of the nuclide 0·5–1·0 mg of Atropine was given to reduce the background activity in the oral cavity by decreasing the salivary secretion.

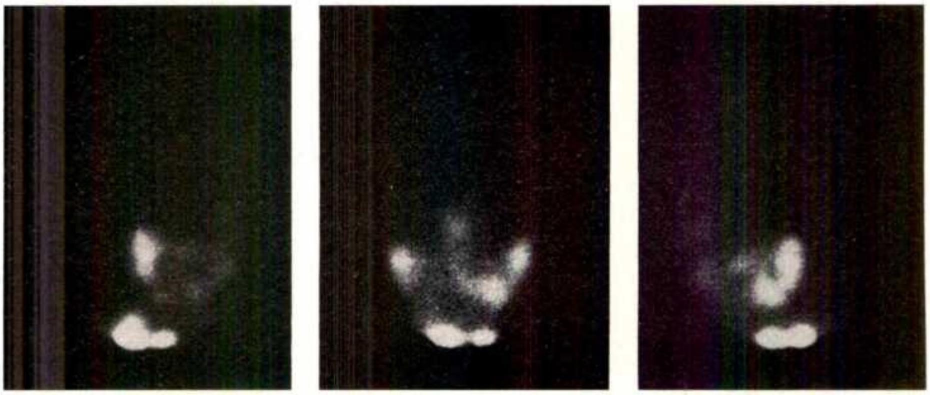
Sequential scintiphotos (Pho-Gamma III, Nuclear Chicago, straight bore collimator, model 812 780) were obtained with 50,000 counts at 20, 60 and 120 minutes after the ^{99}Tc^{m}O$_4$ injection. Additional high efficiency views with 400,000 counts were taken when abnormalities of the glands could be palpated (Fig. 1).

Using a video-recorder, the uptake was registered within the abnormal and contralateral normal gland in 65 patients during the first 30–60 minutes after the ^{99}Tc^{m}O$_4$ injection. Two identical regions of interest covering the area of the glands were employed. These regions had been calibrated under constant geometrical conditions with a ^{57}Co reference source at a distance of three metres. The impulse rates in both regions did not differ by more than 0·5 per cent. The regions were positioned over the individual glands when the entire examination was played back from the video-recorder. The counts were transferred to a linear integrating ratemeter connected to a two-channel pen recorder (Fig. 2).

For rectilinear scanning, a Magna Scanner (Picker) or a Scintimat II (Siemens) were used. Both scanners were equipped with low energy honeycomb collimators (Picker, model 2111A and Siemens, model T II). Colourscans were obtained in the frontal, right and left oblique projections 30 minutes after an injection of ^{99}Tc^{m}O$_4$.

A blind test was performed to assess the clinical value of the sialographic versus the scintigraphic procedure. One physician (G.L.), experienced in sialography, examined all radiographs. Another physician (M.W.S.), experienced in nuclear medicine, examined all scintiphotos and colourscans. Neither physician had any clinical information relating to the patients.

The sialographic diagnosis was considered correct if it was correctly attributed to one of the following



right oblique
400,000 Imp./217″

frontal
400,000 Imp./264″

left oblique
400,000 Imp./272″

FIG. 1.

High efficiency views of salivary glands 20 minutes after injection of one mCi of $^{99}\text{Tc}^{\text{m}}\text{O}_4$, demonstrating absence of uptake by the right submandibular gland secondary to chronic sialolithiasis.

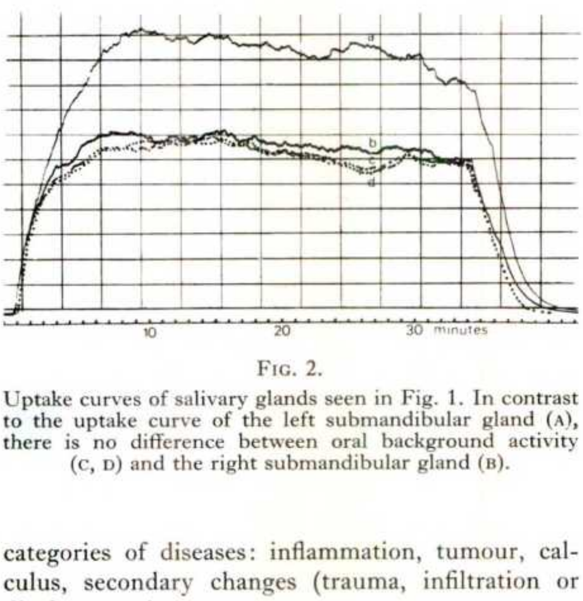


FIG. 2.

Uptake curves of salivary glands seen in Fig. 1. In contrast to the uptake curve of the left submandibular gland (A), there is no difference between oral background activity (C, D) and the right submandibular gland (B).

categories of diseases: inflammation, tumour, calculus, secondary changes (trauma, infiltration or displacement).

The scintigraphic diagnosis was considered correct if any abnormal finding was noted.

A further attempt was made to increase the diagnostic value of the sequential scintiphotos by recording uptake curves from each gland separately and to detect differences by integrating these curves.

PATIENTS

From the local ENT-clinic (W.W.), 191 patients were referred with suspected salivary gland diseases. Seventy-eight cases, including all tumours and secondary gland changes, were confirmed by histology. In 91 cases the clinical course was consistent with the suspected diagnosis. These cases are listed in Table I. Twenty-two cases were excluded from the study as the suspected diagnosis could not be substantiated.

RESULTS

By the accepted criteria, sialograms were correctly interpreted in 80 per cent and scintigrams in 67 per cent of all cases. The various types of isotope uptake are demonstrated in Table II. The proportion of correct diagnoses was raised to 93·5 per cent in sialograms (including six technical failures) and to 86·4 per cent in scintigrams, when the clinical information was taken into account.

Uptake curves of normal and abnormal glands are compared in Table III. The differences are statistically significant. The ratio of radioactivity in glandular tissue to the background of the neighbouring tissues was 2·1 for the parotid gland and 1·9 for the submandibular gland.

DISCUSSION

Examination of the salivary glands by sialography reveals the detailed morphology of the duct system. Scintigraphy appears to be a useful procedure to evaluate the functional status.

The present study was designed to explore the diagnostic value of these two methods. The requirements for a correct scintigraphic diagnosis were

TABLE I

DIAGNOSTIC ACCURACY OF SIALOGRAPHY AND SCINTIGRAPHY

Diseases	Correct sialographic interpretations	Correct scintigraphic interpretations
1. Inflammation (acute, 4; subacute, 18; chronic, 53)	71/75	62/75
2. Malignant tumours (adenocarcinoma, 5; cylindroma, 2; squamous cell carcinoma, 2; malignant pleomorphic adenoma, 1; undifferentiated carcinoma, 1)	11/11	11/11
3. Benign tumours		
Pleomorphic adenoma	23/23	22/23
Warthin's tumour	9/10	9/10
Others (adenoma, 2; intraglandular epidermoid cyst, 2; epithelioma, 1)	4/5	4/5
4. Calculi	30/33	28/33
5. Secondary changes of the glands (displacement by tumour, trauma and inflammation, 7; infiltration and metastases of other primary tumours, 4; sequelae of radiation therapy, 1)	10/12	10/12

TABLE II

PATTERNS OF ISOTOPE ACCUMULATION IN VARIOUS DISEASES

Diseases	Inflammation	Malignant tumours	Benign tumours			Calculi	Secondary changes of the glands
			Pleomorphic adenomas	Warthin's tumours	Others		
Patterns of uptake (comparison of individual glands)	75	11	23	10	5	33	12
1. Equal uptake	13	—	1	1	1	5	2
2. Increased uptake	36	2	8	9	1	4	4
3. Decreased uptake	19	3	5	—	1	14	5
4. Enlargement	5	—	—	—	—	1	1
5. Retention	—	—	1	—	—	3	—
6. Filling-defect	2	6	8	—	2	—	—
7. No uptake	—	—	—	—	—	6	—

TABLE III

MEAN VALUES AND STANDARD DEVIATIONS OF THE RELATIVE DIFFERENCES OF THE UPTAKE CURVES OF NORMAL AND ABNORMAL PAROTID AND SUBMANDIBULAR GLANDS

Parotid glands			Submandibular glands		
Normal	Abnormal	p	Normal	Abnormal	p
(n=13) 1·0±0·7	(n=22) 2·6±1·6	— ≤0·005	(n=10) 1·0±0·7	(n=20) 2·4±1·5	— ≤0·005

considerably lower than for the correct interpretation of sialograms. Nevertheless there were only 86·4 per cent correct diagnoses with scintigraphy but 93·5 per cent with sialography. Gates (1972) found a similar proportion of correct scintigraphic diagnoses. Criteria for a correct diagnosis however, were not stated. We also attempted to relate the pattern of radionuclide uptake to several categories of diseases. In benign tumours, a preponderance of increased uptake was noted in nine out of ten Warthin's tumours. This finding corroborates the results of several investigators (Stebner *et al.*, 1968; Abramson *et al.*, 1969; Münzel, 1970; Gates, 1972).

The remaining benign tumours did not exhibit a predominating pattern of isotope uptake.

In the majority of malignant tumours, decreased uptake and filling defects were observed. These results support, to some degree, the conclusion of Gates (1972), that scintigraphy is useful for the detection of occult neoplasms and the differentiation of benign and malignant tumours.

Schall *et al.* (1972) found a significant difference between uptake curves of normal and abnormal glands. Our comparison of normal and abnormal uptake curves, with a larger number of patients, is consistent with these results.

Objections to the diagnostic relevance of isotope uptake curves are based on differences in the size of individual glands (Ericson, 1972).

Differences in individual gland sizes may further influence the results obtained with uptake curves in combination with clearance studies (Lind and Söderborg, 1970). The diagnostic value of scintigrams, therefore, cannot be improved by additional recording of uptake curves.

REFERENCES

ABRAMSON, A. L., LEVY, L. M., GOODMAN, M., and ATTIE, J. N., 1969. Salivary gland scintiscanning with technetium 99 m pertechnetate. *Laryngoscope, 79,* 1105–1117.

BÖRNER, W., GRÜNBERG, H., and MOLL, E., 1965. Die szintigraphische Darstellung der Kopfspeicheldrüsen mit Technetium 99 m. *Medizinische Welt, 42,* 2378–2380.

ERICSON, S., 1972. Size of the normal parotid gland. *Acta Radiologica (Diagnosis), 12,* 69–75.

GATES, G. A., 1972. Radiosialographic aspects of salivary gland disorders. *Laryngoscope, 82,* 115–130.

LIND, M., and SÖDERBORG, B., 1970. Radiosialometry, a new test of salivary gland function. In *Dynamic Studies with Radioisotopes in Medicine*, pp. 93 (International Atomic Energy Agency, Vienna).

MÜNZEL, M., 1970. Die Diagnostik von Parotistumoren mittels Sialographie und Szintigraphie – eine Gegenüberstellung. *Zeitschrift für Laryngologie, Rhinologie, Otologie und ihre Grenzgebiete, 49,* 607–611.

SCHALL, G. L., LARSON, S. M., ANDERSON, L. G., and GRIFFITH, J. M., 1972. Quantification of parotid gland uptake of pertechnetate using a gamma scintillation camera and a "Region-of-Interest" system. *Radiology, 115,* 689–697.

STEBNER, F. C., EYLER, W. R., and DU SAULT, L. A., 1968. Identification of Warthin's tumour by scanning of salivary glands. *American Journal of Surgery, 116,* 513–517.

WHITE, I. L. 1974. Submandibular gland sialoangiography in the differential diagnosis of lesions of the submandibular triangle. *American Journal of Surgery, 128,* 539–542.

Book review

Tomography of the Temporomandibular Joint. By Olof Eckerdal, pp. 107, 1973 (*Acta Radiologica, Supplementum 329*). (Stockholm), Sw.Kr.40.

This work is essentially a critical analysis of the tomographic image of the cadaver specimen of the mandibular joint in the closed-mouth position, and a carefully-assessed correlation between the image and histological sections in a three-dimensional system.

The material examined consisted of 27 autopsy specimens, carefully frozen to avoid distortion, and set up in a reference system visible in both radiographs and in histological sections.

The work goes into great detail over the correlation between the hypocycloidal tomographic image and joint anatomy, with particular reference to distortion phenomena and false images due to the blur pattern.

Analysis of the parts of the joint accessible for diagnosis by tomography shows that under favourable circumstances the central two-thirds of the joint region is clearly reproduced. Medially and laterally there are zones of increasing blur. These zones are shown to be broader medially, largely because of superimposition from the base of the skull. The author states that blurring is not only due to superimposition from lateral or medial extra-articular parts, but also to geometric-morphologic factors within the joint. Tomographic layer thickness, distortion, superimposition of incompletely blurred entities, spurious images and detail reproduction have been investigated.

This work should certainly be consulted by the radiologist faced with difficulty over the interpretation of the tomographic images of the anatomy of the mandibular joint.

W. CAMPBELL.

1976, *British Journal of Radiology*, *49*, 330–334

Computer subtraction in regional cerebral blood-volume measurements using the EMI-Scanner

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(*Received September, 1975*)

ABSTRACT

A computerized subtraction technique has been described to measure regional cerebral blood volume (rCBV) using the EMI-Scanner in a group of 13 patients. Sodium iothalamate was injected intravenously (1·75 ml./kg) to increase the absorption of X rays in the cerebral circulation. Significant regional differences in CBV were shown, values in the frontal and temporal regions being lower than the mean hemisphere value (4·9 ± 0·7) and higher in the occipital region. The left hemisphere showed a significantly higher CBV when compared with the right. Measurements of CBV in the cortex showed no regional variation, but the mean cortical value of 6·0 ± 1·8 was significantly higher than the hemisphere mean.

Regional cerebral blood volume (rCBV) is difficult to measure by non-invasive methods. Grubb *et al.* (1973) used a method involving the X-ray fluorescence of injected iodine for estimations of rCBV in patients in the posterior frontal region. The sampling areas, however, cannot be as well defined as is possible when using the EMI-Scanner. By selecting data from slices at different transverse levels in the head, anatomical and pathological structures can easily be identified (Ambrose, 1973). Therefore it is possible, using the EMI-Scanner, to relate rCBV to a particular anatomical structure. This method of rCBV measurement in the cortex and thalamus has been described in a recent communication (Ladurner *et al.*, 1975). In the present paper we assess how the accuracy of the method might be improved by a computerized subtraction technique which can be applied to measurements both in small and large areas of the brain.

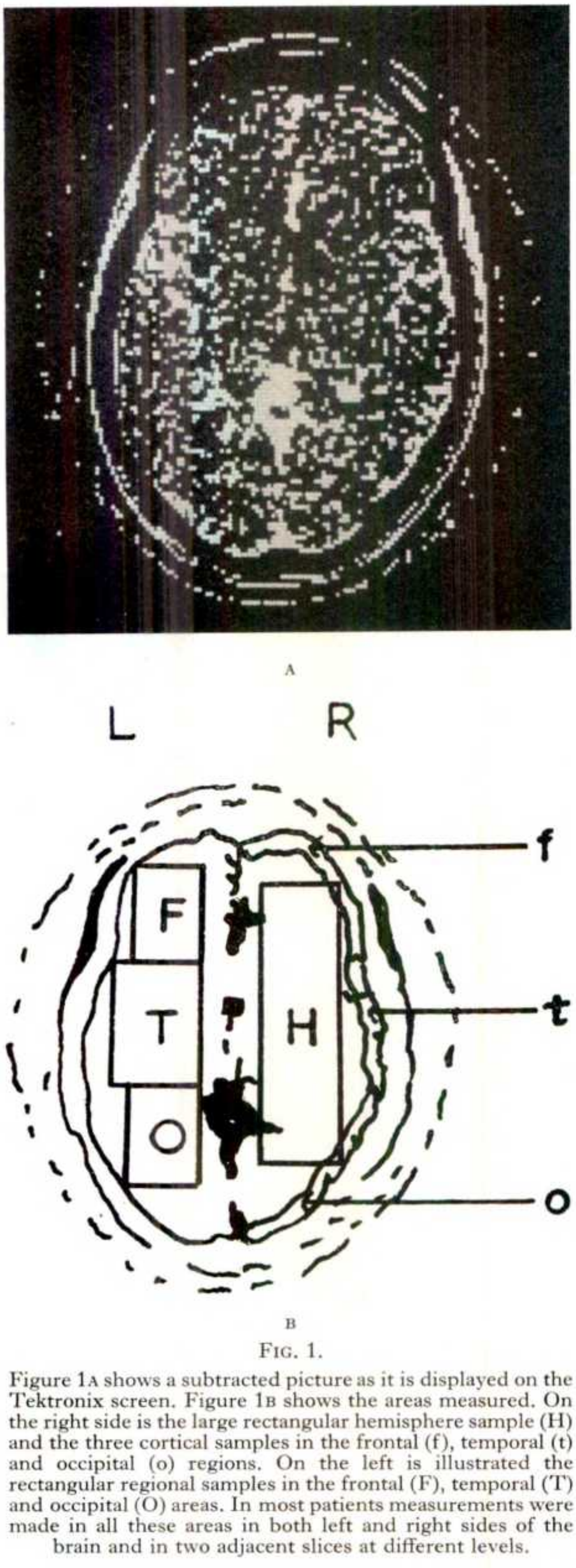
METHODS

rCBV measurements were made in 13 patients including four with normal EMI-scans, two patients with transient ischaemic attacks with normal scans, four cases of multi-infarct dementia (Hachinski *et al.*, 1975), two patients with completed strokes, and one with a tumour. The method of rCBV estimation has already been described in detail (Ladurner *et al.*, 1975), and will only be summarized here.

In the EMI-scans two cuts (referred to as 2A and 2B) 43 and 56 mm respectively above the orbitomeatal line were made and repeated after the intravenous injection of sodium iothalamate (Conray 420) in a mean dose of 1·75 ml./kg bodyweight. Blood samples were taken from the contralateral arm vein at intervals of one, three and five minutes during the six and a half minute scan which started as soon as the injection was completed. The concentration of sodium iothalamate in these samples was estimated by a spectrophotometric method in eight patients (Purkiss *et al.*, 1968) and by phantom studies using the EMI-Scanner in five patients. The blood iothalamate concentration values were averaged to obtain a mean for the scanning period. rCBV was calculated as in the previous paper except that the EMI data was processed by computer. For the calculation of rCBV, the EMI numbers before and after the introduction of sodium iothalamate, its concentration in the blood and the patient's haematocrit were required. The system for processing the data consisted of a Varian 73 computer equipped with 12K 16-bit words of core memory, a cartridge disc unit, a seven-track IBM compatible magnetic tape unit, a Tektronix 4010 terminal and a teletype.

The outlines of the patient's skull obtained from the two EMI-scans were displayed on the Tektronix screen and the operator superimposed the two outlines exactly by vertical, horizontal and rotational adjustments. When patients remained completely still, little or no adjustment was necessary for good superimposition. The computer then subtracted the pre-injection from the post-injection scan and the resultant subtracted picture was displayed on the screen. From the picture an area of any desired shape and size was selected using the cross hairs on the screen of the terminal and the computer then calculated the mean difference in EMI number for that area. The mean value, its SD, SE and number of EMI matrix cells were shown on the screen and printed out by the teletype.

Figure 1 shows both a subtracted picture and how the areas selected for measurement were standardized. Frontal (f), temporal (t) and occipital (o) measurements were made in the superficial layer



A

B

FIG. 1.

Figure 1A shows a subtracted picture as it is displayed on the Tektronix screen. Figure 1B shows the areas measured. On the right side is the large rectangular hemisphere sample (H) and the three cortical samples in the frontal (f), temporal (t) and occipital (o) regions. On the left is illustrated the rectangular regional samples in the frontal (F), temporal (T) and occipital (O) areas. In most patients measurements were made in all these areas in both left and right sides of the brain and in two adjacent slices at different levels.

which was considered to be largely grey matter. These areas consisted of 100–300 EMI matrix cells ($1{\cdot}5 \times 1{\cdot}5 \times 13$ mm) representing between 2·9–8·7 cm^3 of tissue. Measurements were also made in three areas which included both grey and white matter (F, T, O in Fig. 1B). The frontal region consisted of 650 EMI matrix cells (19 cm^3), the temporal of 1,150 EMI matrix cells (34 cm^3) and the occipital of 750 EMI matrix cells (22 cm^3). Measurements of the whole hemisphere contained 2,200 EMI matrix cells or 64 cm^3 of tissue. Areas containing artefacts, large sulci and ventricles were avoided. For each scan there were two adjacent slices (2A and 2B) and results from the corresponding areas in each were combined to give a mean. Where measurements were made in both hemispheres, not only slice A and B but also data from the right and left were combined to give a mean value. In the two patients with transient ischaemic attacks (TIA) only the hemisphere corresponding to the clinical signs was included in the rCBV measurements in the group of patients with vascular disease. The opposite hemisphere was included in the normals.

RESULTS

Normals

The rCBV results for the patients with normal EMI-scans are shown in Table I. The mean cortical value was 6·0 ml./100 ml. of tissue and was significantly higher than the mean hemisphere value ($p=0{\cdot}05$). Cortical blood volumes in the frontal, temporal and occipital regions did not vary significantly from the cortical mean. CBV in the temporal cortex was significantly higher than in the temporal lobe as a whole ($p=0{\cdot}025$), but this was not so in the occipital and frontal regions.

The data in Table I also show there were highly significant differences in blood volume between lobes ($p<0{\cdot}02-<0{\cdot}005$). The measured hemisphere value was 4·9 ml./100 ml. which compares well with the mean of the three lobar values which was 4·6 ml./100 ml. The frontal blood volume was significantly lower ($p<0{\cdot}005$) than the hemisphere mean, as was the temporal value ($p<0{\cdot}05$), whereas the volume in the occipital lobe was significantly higher ($p<0{\cdot}02$) than the hemisphere mean.

Table II shows relative standard deviations for the measurements ranging from 13 per cent in the temporal lobe to 26 per cent in the frontal lobe. One reason for the considerably higher figure in the frontal region is that measurement is difficult, particularly in the cortex because of the proximity of bone and its curvature. In the second line we have

TABLE I

RCBV (ML./100 ML.) IN PATIENTS WITH NORMAL EMI-SCANS

No.	Final diagnosis	Mainly grey matter				Grey and white matter			
		Frontal	Temporal	Occipital	Mean	Frontal	Temporal	Occipital	Hemisphere
1	Dystortion dystonia	2·4	7·7	4·3	4·8	3·5	4·1	5·0	4·4
2	Hemi Parkinsonism	6·6	6·4	4·4	5·8	3·7	4·7	4·4	4·5
3	Disseminated sclerosis	2·3	5·3	6·3	4·6	2·9	3·9	5·4	4·4
4	Infratentorial tumour	7·2	7·2	6·7	7·0	4·2	5·0	6·0	5·1
5	Transient ischaemic attacks	9·0	9·6	8·6	9·1	5·8	5·5	7·6	6·3
6	Transient ischaemic attacks	5·7	3·7	5·1	4·8	3·1	4·2	5·5	4·6
	Mean	6·2	6·7	5·9	6·0	3·9	4·6	5·6	4·9
	SD	2·5	2·0	1·6	1·8	1·0	0·6	1·0	0·7

TABLE II

STANDARD DEVIATIONS OF RCBV COMPARED WITH THOSE OBTAINED FROM THE REGIONAL PATTERN OF CBV IN THE NORMAL GROUP

	Grey and white matter		
	Frontal (SD)	Temporal (SD)	Occipital (SD)
Mean rCBV (ml./100 ml.)	3·9 (26)*	4·6 (13)*	5·6 (18)*
Mean % of hemisphere (pattern)	79 (10)	94 (6)	115 (9)

*SD is the relative SD as a % of the mean.

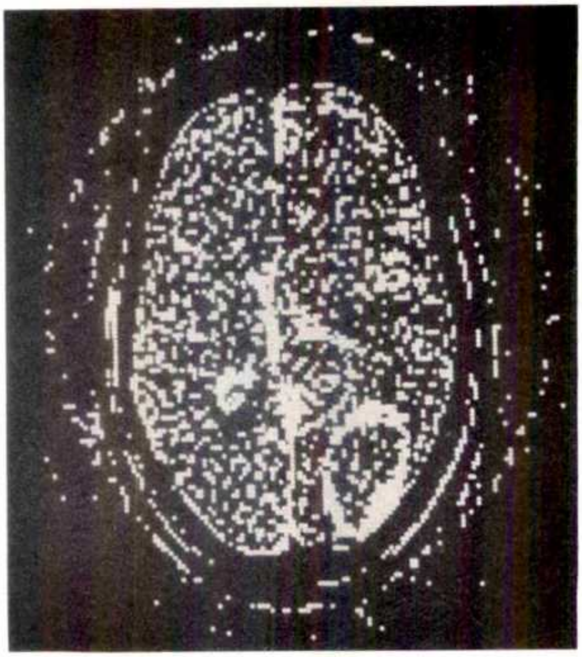


FIG. 2.

Figure 2 shows the subtracted picture obtained from scans in a patient with a tumour in the right occipital region. Note how well the highly vascular capsule of the tumour is defined.

expressed the regional values for each patient as a percentage of his hemisphere value to try to eliminate patient to patient variation and scan to scan variation. The considerable reduction in standard deviations would seem to indicate that these two factors make a large contribution to the standard deviations in line 1.

Blood volume was compared for the right and left cortex and hemispheres in the four normal patients (all of whom were right handed) in whom data from both hemispheres was available. The results are shown in Table III. There was a significantly higher volume in the left hemisphere ($p < 0{\cdot}02$). Blood volume in the cortex was only significantly higher in the left temporal area ($p < 0{\cdot}02$).

Patients with cerebrovascular disease

In the four patients with multi-infarct dementia, two patients with TIAs and two with completed strokes, abnormal areas were avoided when making the measurements; it was found that the lobar and hemisphere CBV values were not significantly different from the normal group (Table IV). The multi-infarct dementia group, however, showed a significantly higher mean cortical blood volume when compared with the normals ($p < 0{\cdot}02$). On a regional basis, no one area was significantly different from the mean in its blood volume.

TABLE III

COMPARISON OF RIGHT AND LEFT rCBV IN FOUR PATIENTS WITH NORMAL EMI-SCANS

	Mainly grey matter				Grey and white matter			
	Frontal	Temporal	Occipital	Mean	Frontal	Temporal	Occipital	Hemisphere
Right	4·9 (2·6)	5·8 (1·1)	4·6 (1·1)	5·1 (0·7)	3·5 (0·2)	3·9 (0·8)	4·5 (0·2)	4·7 (0·9)
Left	4·3 (3·0)	7·4 (1·0)	6·2 (2·0)	6·0 (1·6)	3·6 (1·1)	5·0 (0·5)	5·5 (0·6)	4·4 (0·5)

TABLE IV

MEAN rCBV IN NORMALS AND PATIENTS WITH VASCULAR DISEASE

		Mainly grey matter				Grey and white matter			
No.	Category	Frontal	Temporal	Occipital	Mean	Frontal	Temporal	Occipital	Hemisphere
4 2	Normals + Normal h/spheres from TIA patients	4·1 (2·5)	6·8 (2·1)	6·0 (1·8)	6·0 (1·7)	4·0 (1·1)	4·7 (0·8)	5·8 (1·2)	5·0 (0·8)
4	Multi-infarct dementia	10·4 (1·4)	8·0 (1·6)	8·2 (1·2)	8·9* (0·9)	4·8 (1·7)	4·8 (1·0)	6·3 (1·1)	5·8 (0·4)
4	T.I.A. + C.S.	5·8 (2·8)	7·3 (4·4)	5·7 (1·7)	6·3 (2·9)	4·3 (1·5)	4·9 (1·1)	5·4 (1·8)	5·1 (1·4)

*$p < 0{\cdot}02$

Patient with cerebral metastasis

Figure 2 shows the subtracted picture at the 2A level in a patient with a tumour in the occipital region. Blood volume calculations gave a mean of 16·7 ml./100 ml. for the tumour as a whole. The capsule showed a high volume (34·7 ml./100 ml.) while the necrotic tissue in the middle had a value of 1·3 ml./100 ml. It is of interest that the oedematous area round the tumour showed a blood volume of 0·4 ml./100 ml., its very low value being a good indication that the sodium iothalamate has remained in the vascular compartment.

DISCUSSION

Regional differences in cerebral blood volume have been found in patients with apparently normal EMI-scans. Measurements in the frontal, temporal and occipital lobes gave significantly different results (Table I). The blood volume in the frontal region (3·9±1·0) is of the same order as that found by Grubb *et al.* (1973), (3·2±0·94), who used an X-ray fluorescence method to measure rCBV in patients in the same area. The cortical value confirms the indications that CBV is higher in the cortex and therefore explains why the value is so much higher than that of Grubb *et al.* (1973) whose sampling area probably contained a mixture of grey and white matter.

The cortical rCBV estimated with the computer subtraction technique is very close to the hand calculated result (5·7±1·6) reported in a previous communication (Ladurner *et al.*, 1975), even though much larger areas were sampled when using the computer subtraction technique.

The accuracy of the measurement is considerable when patient to patient variation and scan to scan variation are eliminated by considering the pattern of rCBV rather than the absolute values (Table II). A larger number of patients with less heterogeneous final diagnoses in the normal group may substantially reduce the errors in the absolute value of rCBV, but the standard deviations as they stand compare favourably with other methods.

The greatest advantage of this method of rCBV estimation is its versatility. There is the possibility of measuring blood volume in a small localized area (as in a tumour), in a distinct type of tissue (cortex or thalamus), or in larger areas—lobes and even hemispheres. Using EMI-scans and the subtraction technique one can compare blood volumes not only between pathological and normal tissue but between right and left hemispheres, and all these from cross sections of the brain at a variety of anatomical levels.

ACKNOWLEDGMENTS

The computer system used for the subtraction technique was provided by the Medical Research Council. Invaluable help was given by the radiographers and Miss B. Cummack in spectrophotometric estimations of plasma sodium iothalamate. We thank Miss B. Laatz for her assistance in the preparation of the manuscript.

REFERENCES

AMBROSE, J., 1973. Computerized transverse axial scanning (tomography): Part 2. Clinical application *British Journal of Radiology*, *46*, 1023–1047.

GRUBB, R. I., PHELPS, M. E., and TER-POGOSSIAN, M. M., 1973. Regional cerebral blood volume in humans. *Archives of Neurology*, *28*, 38–44.

HACHINSKI, V. C., ILIFF, Linnette D., ZILKHA, E., DU BOULAY, G. H., MCALLISTER, V. L., MARSHALL, J., ROSS RUSSELL, R. W., and SYMON, L., 1975. Cerebral blood flow in dementia. *Archives of Neurology 32*, 632–637.

LADURNER, G., ZILKHA, E., ILIFF, Linnette D., DU BOULAY, G. H., and MARSHALL, J., 1976. Measurement of regional cerebral blood volume by computerised axial tomography. *Neurology, Neurosurgery and Psychiatry* (in press).

PURKISS, P., LANE, R. D., CATTELL, W. R., KELSEY FRY, I., and SPENCER, A. G., 1968. Estimate of sodium diatrizoate by absorption spectrophotometry. *Investigative Radiology*, *3*, 271–274.

Book review

Stress Fractures. By Michael Devas, pp. viii+240 (Edinburgh, London and New York, Churchill Livingstone), £15·00.

There can be few radiologists who have not at some time agonized over the problem of diagnosis in a young person presenting with limb pain, local swelling and accompanied by radiographic evidence of periosteal reaction with subtle underlying bone change. When this picture results from stress fracture, the author emphasizes that the diagnosis should be made clinically in the first instance, with radiographs taken for confirmation. The book is written from the clinician's viewpoint and after a unique experience of the subject following long personal association with the Middlesex Hospital Stress Fracture Bureau. Mr. Devas is to be congratulated on the pure distillation of the essence of so many illustrative cases and its presentation in such a palatable form.

Stress fractures occur in normal healthy people occupied in normal activity, although it should be recognized that invariably this is of unusual nature. The immediate cause of bone failure is the application of a degree of muscle power which is disproportionate to underlying bone strength. A careful history is vital, and in a medico-legal context, it is of considerable practical importance for radiologists to be aware that children barely old enough to walk can, with no injury, break the tibia or fibula.

Individual anatomical sites subject to stress fracture are considered in great detail under separate chapters. A fine blend of comprehensive and yet practical information is presented, which has been perceived through the eyes and hands of a skilled clinician. Radiologists will appreciate the use of radiographic "tricks of the trade" which may elucidate difficult problems when viewed in the light of clinical examination. For completeness, there are two additional sections from the veterinary field illustrating comparative injuries which occur in horses and greyhounds.

The bibliography, which is both comprehensive and up to date, is given at the end of the book in a separate chapter. This is an attractive feature enabling continuity of thought for the reader without distraction.

Considering the difficulty in demonstrating subtle radiological signs on the original radiograph the standard of reproduction of the illustrations is of a very high order. It is noted that Figures 32 and 35, showing an example of a healing fracture of the pars interarticularis of a lumbar vertebra, appear to have been inadvertently transposed.

The book is warmly commended to every radiologist who is concerned with the diagnosis of this type of problem.

W. M. PARK.

1976, *British Journal of Radiology*, *49*, 335–338 APRIL 1976

Regional blood flow in human tumours with special reference to the effect of radiotherapy*

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(*Received June, 1975*)

ABSTRACT

Blood flow in 41 superficial tumour nodules, of which nine were lymphomas, nine anaplastic carcinomas and 23 differentiated malignomas was measured using the ^{133}Xe-clearance method. The lymphomas showed statistically higher blood flow (38·4 ml./min/100 g) than anaplastic (11·4 ml./min/100 g) and differentiated tumours (13·7 ml./min/100 g). After one week of radiation treatment the mean blood flow in anaplastic carcinomas was higher than the initial value. After an interval following the end of the radiation treatment the circulation diminished significantly compared with that observed immediately at the end of radiotherapy. The size of the tumours did not correlate with the blood flow.

The effect of irradiation depends on the oxygen concentration of the tissue (Gray *et al.*, 1953; Thomlinson, 1967). The main factors in the maintenance of oxygen tension are the vascularity, oxygen consumption and blood flow. The radiotherapy of tumours causes changes in the blood flow. Several workers have made microangiographic and histological studies on the effect of radiation on tumours and have studied the oxygen tension in tumours in the course of radiotherapy (Badib and Webster, 1969; Horn *et al.*, 1974; Gump and White, 1968; Kallman *et al.*, 1970; Reinhold, 1971; van Putten and Kallman, 1968; Du Sault, 1969; Kruuv *et al.*, 1967). Only a few authors have examined quantitatively blood flow in tumours. The ^{133}Xe-clearance method offers an easy and quantitative method for the measurement of perfusion especially in superficial tumours (Tanaka, 1974; Bru *et al.*, 1970).

The purpose of this work is to elucidate the blood flow in different types of superficial tumours in man using the ^{133}Xe-clearance method. The changes in flow were measured during and after radiotherapy. The correlation of the perfusion rate with the tumour size and radiosensitivity are considered.

MATERIAL AND METHODS

Forty-one superficial tumour nodules in 32 patients were measured. The tumours were classified under three types: lymphomas, anaplastic carcinomas and differentiated malignomas. The tumours studied are listed in Table I. Histological verification was made in all cases.

The radiation treatment to the nodule area was given in 23 cases with a ^{60}Co-unit (Siemens Gammatron 3), in four cases with 10 MeV electrons from a betatron (Medical Betatron B5–25) and in two cases with X rays. The irradiation was given in five fractions per week; the weekly dose varied from 1,100 to 3,000 rads. Some patients had, in the course of the radiation period, a two to three weeks rest interval.

^{133}*Xe measurements*

^{133}Xe dissolved in 0·9 per cent saline was used as a tracer (half life 5·3 days; gamma ray energy 81 keV). A volume of 0·1 ml. (100–200 μCi) was slowly injected (needle No. 20) into the middle of the nodule studied. The rate of disappearance of the tracer was followed for 15–20 minutes with a collimated NaI(Tl) scintillation detector. The counts were registered in digital form with a multichannel analyzer (DIDAC 800). The channel width used was 10 seconds and the diameter of the measuring field was 10 cm.

A minicomputer (NOVA 1220) was used in the calculations. A two-exponential curve ($Ae^{-k_1t}+Be^{-k_2t}$) was fitted to the measured counts using the iterative least squares method. A typical curve is presented in Fig. 1. The local blood flow was calculated from the equation

$$F=\lambda\frac{Ak_1+Bk_2}{A+B}$$

where the terms k_1 and k_2 are the dissappearance rate constants and A and B the corresponding scale constants for the exponential terms. The factor λ is the partition coefficient (100 ml./100 g) (Tanaka, 1974) between nodule tissue and blood. The partition coefficient depends strongly on the fat content of the tissue and slightly on the haematocrit. This can cause an error in the absolute results. When following the blood flow changes during radiotherapy in same patients this systematic error, however, has only a slight significance.

The Xe-clearance method used here is easy and applicable to blood flow measurements in superficial tumours. The reproducibility of the method

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*Read at Congressus tertius societatis radiologicae europaeae Edinburgh, June 26, 1975.

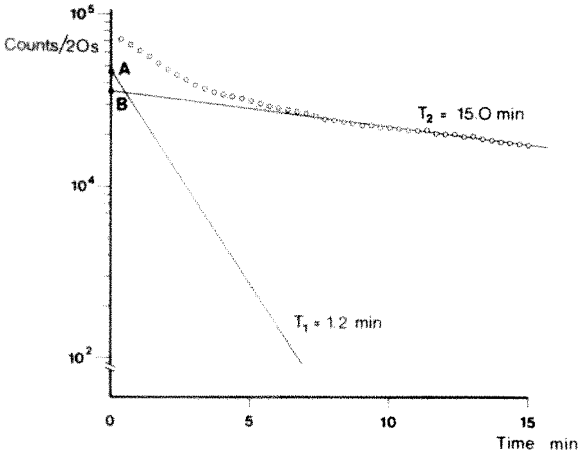

FIG. 1.

Typical ^{133}Xe disappearance curve divided into two components. The disappearance rate constants $k_{1,\,2} = \frac{0.693}{T_{1,\,2}}$.

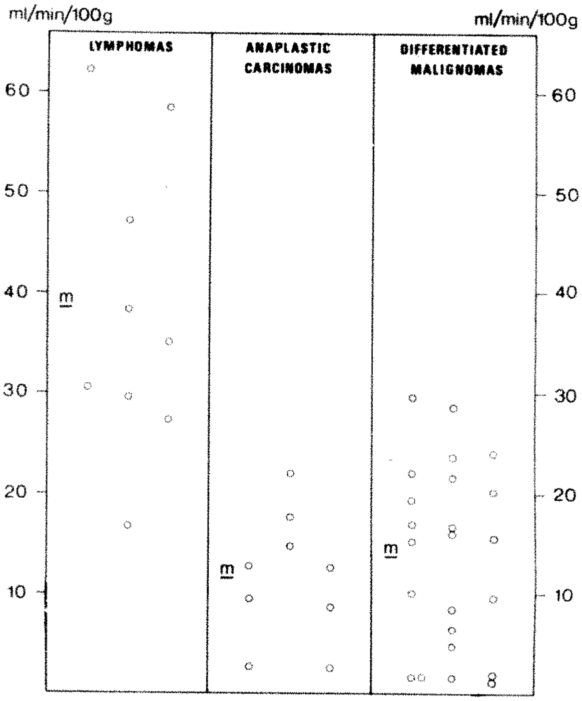

FIG. 2.

Blood flow values in different tumour groups. The mean is marked by *m*.

is adequate (about ±2 ml./minute/100 g). It must be noted, however, that the clearance method gives the blood flow value locally from the site of injection. In tumours there can be differing circulation in different parts of the nodule. For example, Xe-injection into the necrotic centre of the tumour shows low circulation compared with the mean blood flow of the nodule.

In the statistical analysis the t-test was used. The ^{133}Xe measurements were made before the radiotherapy and in 28 cases after one week's treatment, in 20 cases after two weeks' treatment and in 17 cases after three weeks' treatment. Fourteen measurements were made one to three weeks after the ending of radiotherapy.

RESULTS

Figure 2 shows the individual flow values in different tumour types. The mean blood flow was 38·4±14·3 ml./minute/100 g in lymphomas, 11·4±5·1 ml./minute/100 g in anaplastic tumours and 13·7±9·0 ml./minute/100 g in differentiated malignomas. Thus there was a highly significant higher blood flow in the lymphomas than in the other types. In the anaplastic and differentiated groups 11 nodules were in areas of earlier irradiation or of surgical operation. The blood flow in these nodules (11·7±8·7 ml./minute/100 g) was lower than in nodules in intact regions (13·4±8·0 ml./minute/100 g) but the difference was not statistically significant.

There was no significant correlation between the size and the local blood flow of nodules. In the anaplastic group there was a significant ($p < 0{\cdot}01$) increase in the blood flow values after one week's radiation (Fig. 3). In the other groups these changes were not significant. After two weeks' irradiation no clear changes were found when compared with the flow values before the radiation.

In 14 patients the blood flow was measured after the end of the radiation treatment (Fig. 4). In eight cases there was a clear decrease in blood flow. In three nodules there was only a slight decrease and in three a slight increase. The mean decrease (from 27·6 to 16·1 ml./minute/100 g) was 42 per cent, which is statistically significant ($p < 0{\cdot}01$).

Figure 5 represents the initial blood flow values (before the radiation) compared with the time when the nodule was diminished to 37 per cent (1/e) of its initial volume. There seems to be a negative correlation between the initial flow values and regression time. The lymphoma data, however, may be part of a different nodule population having a higher blood flow and conclusions relating regression and blood flow are uncertain.

The changes in the blood flow during the radiation treatment did not correlate with the regression of the tumours.

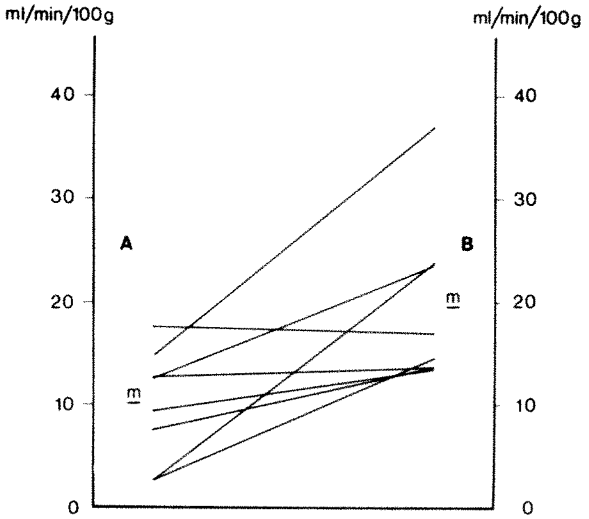

Fig. 3.

Blood flow in anaplastic carcinomas before (A) and after (B) one week's treatment. The mean is marked by *m*.

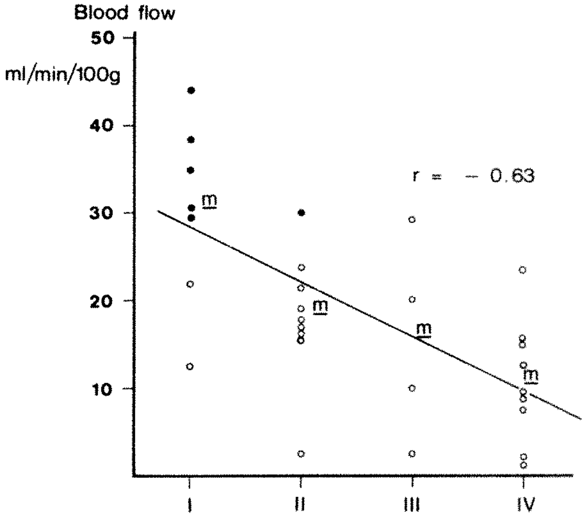

Fig. 5.

The dependence of regression time of tumours (diminishing to 37 per cent of the initial size) on blood flow before irradiation:

I in less than one week;
II in one to two weeks;
III in two to three weeks;
IV in over three weeks or only slight regression.

lymphomas (●); other malignomas (○). *m* marks mean value of each group.

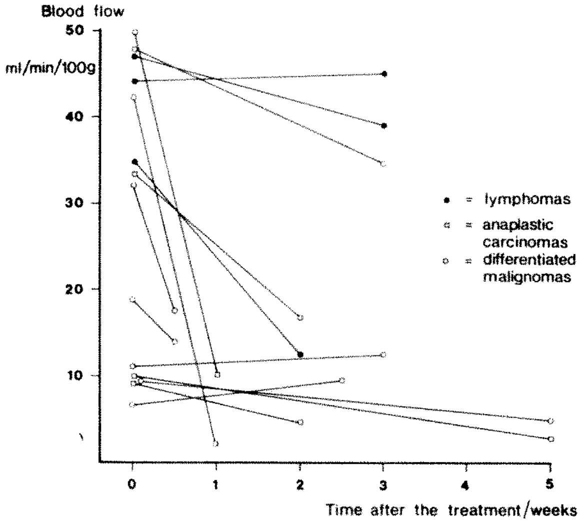

Fig. 4.

Blood flow values at the end of treatment period and 0·5–4 weeks later without irradiation.

Discussion

Most of the studies concerning blood flow in tumours have been performed in animals. In this work the measurements have been done entirely on human tumours. Therefore, the measurements are restricted to the superficial nodules. There was a distinctly higher blood flow in the lymphomas than in the other tumours (anaplastic and differentiated). This result agrees with some single observations of Tanaka (1974) and Bru *et al.* (1970).

Nodules which were in previously irradiated or operated areas had lower circulations than nodules in intact areas. Obviously the scar formation in the tumour bed caused a small decrease also in tumour circulation.

The size of the nodules did not correlate with the blood flow values, which contradicts the results of Tanaka (1974). In Tanaka's work, however, the experimental tumours measured were clearly smaller than the human tumours studied in the present work.

Badib and Webster (1969) measured pO_2 values in tumours during the course of radiotherapy. In their work there was a constant increase in pO_2 to the fourth week of radiation. The blood flow changes in our work seem to be in agreement with the pO_2 measurements of Badib and Webster in the first week of radiation. During and after the second week, however, there was no increase in the blood flow values.

After the end of the radiation treatment there was a decrease in the rate of perfusion. The decrease was greatest in the cases where measurements were made

TABLE I.

Types and origins of tumours studied

Histological "diagnoses"	Number of patients	Number of nodules
Lymphomas		
Lymphosarcoma	4	5
Reticulum cell sarcoma	1	1
Malignant lymphomas	2	3
Anaplastic carcinomas		
Cancer of the lung	2	2
Cancer of the thyroid	2	2
Cancer of the prostate	1	1
Cancer of the breast	1	1
Cancer of the pancreas	2	3
Differentiated malignomas		
Differentiated squamous cell carcinoma of the lung	5	8
Adenocarcinoma of the breast	7	7
Adenocarcinoma of the colon	1	4
Adenocarcinoma of the prostate	1	1
Adenocarcinoma of the parotid gland	1	1
Follicular carcinoma of the thyroid	1	1
Metastatic malignant melanoma	1	1

a week after the end of irradiation. From measurements performed three weeks after, or later, it was found that the circulation was nearly the same as at the end of radiation. It seems that during the first stage after the end of treatment the degenerative vascular process continues but this is followed by recovery later.

Carcinomas which arise in scar tissue, cystic tumours, recurrent tumours, after irradiation or surgical operation, and large tumours are radioresistant and show low tumour blood flow. The changes in the vascular system after or during the course of irradiation can obviously influence the effect of the administration of anticancer drugs. It seems important to increase (with different agents or fractionation modes) the blood flow within tumours, in order to improve oxygenation and enhance the effects of chemotherapy and radiotherapy.

Acknowledgment

This work was supported in part by the Radiological Society of Finland.

REFERENCES

Badib, A. O., and Webster, J. H., 1969. Changes in tumor oxygen tension during radiation therapy. *Acta Radiologica, Therapy Physics Biology*, *8*, 247–257.

Bru, A., Combes, P. F., Douchez, J., Lucot, H., and Ribot, J. F., 1970. Estimation de l'activité circulatoire a l'intérieur des tumeurs ganglionnaires malignes par la mesure du taux d'épuration du xénon-133. Etude des modifications sous radiothérapie. In IAEA proceedings of a symposium on *Dynamic Studies with Radioisotopes in Medicine*, Rotterdam 1970, pp. 633–642.

Du Sault, L. A., 1969. Reoxygenation of tumors during radiotherapy. *Radiology*, *92*, 626–628.

Gray, L. H., Conger, A. D., Ebert, M., Hornsey, S., and Scott, O. C. A., 1953. The concentration of oxygen dissolved in tissue at the time of irradiation as a factor in radiotherapy. *British Journal of Radiology*, *26*, 638–647.

Gump, F. E. and White, R. L., 1968. Determination of regional tumor blood flow by krypton-85. *Cancer*, *21*, 871–875.

Horn, N. L., Thompson, M., Howes, A. E., Brown, J. M., Kallman, R. F., and Probert, J. C., 1974. Acute and chronic effects of X-irradiation on blood flow in mouse limb. *Radiology*, *113*, 713–722.

Kallman, R. F., Jardine, L. J., and Johnson, C. W., 1970. Effects of different schedules of dose fractionation on the oxygenation status of a transplantable mouse sarcoma. *Journal of the National Cancer Institute*, *44*, 369–377.

Kruuv, J. A., Inch, W. R., and McCredie, J. A., 1967. Blood flow and oxygenation of tumors in mice. *Cancer*, *20*, 51–70.

Reinhold, H. S., 1971. Improved microcirculation in irradiated tumours. *European Journal of Cancer*, *7*, 273–280.

Tanaka, Y., 1974. Regional tumor blood flow and radiosensitivity. In *Fraction Size in Radiobiology and Radiotherapy*, pp. 13–26, eds. Sugahara, Révész, Scott. (Urban and Schwarzenberg, München-Berlin-Wien; Igaku Shoin Ltd., Tokyo).

Thomlinson, R. H., 1967. Oxygen therapy—Biological considerations. In *Modern Trends in Radiotherapy*, pp. 52–72, eds. Deeley and Wood. (Butterworths, London).

Van Putten, L. M., and Kallman, R. F., 1968. Oxygenation status of a transplantable tumor during fractionated radiation therapy. *Journal of the National Cancer Institute*, *40*, 441–451.

1976, *British Journal of Radiology*, *49*, 339–343

APRIL 1976

The continuous inhalation of Oxygen-15 for assessing regional oxygen extraction in the brain of man

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(Received November, 1974 and in revised form September, 1975)

ABSTRACT

A non-invasive steady-state method for studying the regional accumulation of oxygen in the brain by continuously inhaling Oxygen-15 has been investigated. Oxygen respiration by tissue results in the formation of water of metabolism which may be considered as the "exhaust product" of respiration. In turn the steady-state distribution of this product may be related to that of oxygen utilization. It has been found in monkeys that an appreciable component of the signal, recorded over the head during the inhalation of $^{15}O_2$, is attributable to the local production of ^{15}O-labelled water of metabolism. In man the distribution of radioactivity recorded over the head during $^{15}O_2$ inhalation clearly relates to active cerebral tissue. Theoretically the respiration product is linearly dependent on the oxygen extraction ratio of the tissue, and at normal cerebral perfusion it is less sensitive to changes in blood flow. At low rates of perfusion a more linear dependence on flow is shown. The dual dependence on blood flow and oxygen extraction limits the interpretation of the cerebral distribution obtained with this technique. Means for obtaining more definitive measurements with this approach are discussed.

The use of a γ-emitting radioisotope of oxygen, detectable external to the body, makes possible a non-invasive means for studying the regional extraction of oxygen in the brain. In this context we have investigated the use of cyclotron produced Oxygen-15. This is the longest-lived γ-emitting isotope of oxygen, and decays by positron emission with a radioactive half-life of 2·1 minutes. Injection of ^{15}O-labelled blood into the carotid artery has previously been used to provide accurate measurements of the regional utilization rate of oxygen in the human brain (Ter-Pogossian *et al.*, 1970; Ter-Pogossian *et al.*, 1971; Carter *et al.*, 1972; Raichle *et al.*, 1975). However, this method has limited clinical application since it is invasive and is performed while the subject is in a somewhat abnormal physiological condition. Furthermore, it rests on measuring the extraction of ^{15}O in a single passage, together with blood flow by washout, following the injection of $H_2{}^{15}O$. It is impractical to make such measurements with high spatial resolution, since currently available imaging devices have an inherently low sensitivity to the 511 keV annihilation emitted by ^{15}O. In addition, clearance methods have a poor resolution for areas with low perfusion. A further disadvantage is that tomography by γ-ray emission (Chesler 1972; Ter-Pogossian *et al.*, 1975) demands a steady state. In order to overcome these limitations we have considered an alternative approach, namely that of continuously inhaling $^{15}O_2$ to equilibrium, and recording the resulting steady-state distribution of radioactivity deposited within the brain.

THEORY

During the tissue respiration of oxygen, hydrogen is donated to produce water of metabolism. Thus the steady state observed while continuously inhaling $^{15}O_2$ may be equated to the local production of $H_2{}^{15}O$ under a condition of "dynamic equilibrium" (Jones *et al.*, 1974). The water of metabolism can be considered as the "exhaust product" of oxygen respiration. Hence the distribution of ^{15}O-labelled water of metabolism ($H_2{}^{15}O_{met.}$), as observed externally, can be related to that of oxygen uptake.

The steady state $H_2{}^{15}O_{met.}$ in the tissue represents a balance between the formation of $H_2{}^{15}O_{met.}$, due to utilization of ^{15}O, and the disappearance of this respiration product through radioactive decay and tissue wash-out by blood flow;

$$\frac{(C_a - C_v)}{Ca} \,.\, Ca^* \,.\, F = (\lambda + F/V)\, H_2{}^{15}O_{met.}$$

Where C_a and C_v are the arterial and venous concentration of stable oxygen, $C_a{}^*$ the arterial concentration of ^{15}O, F the tissue blood flow, V the tissue volume and λ the radioactive decay constant

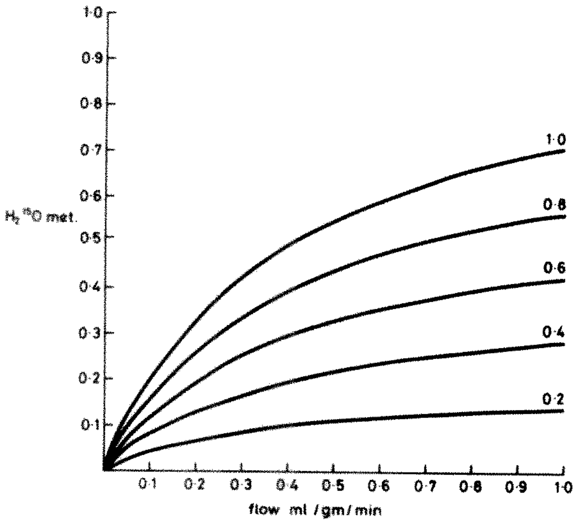

Fig. 1.

Dependence of the concentration of $H_2{}^{15}O_{met.}$ on tissue blood flow for five oxygen extraction ratios (0·2–1·0).

for ^{15}O. The term $\frac{(C_a-C_v)}{Ca}$ is the oxygen extraction ratio for the tissue. Thus, at equilibrium, the ^{15}O-labelled water of metabolism is proportional to the utilization rate of ^{15}O (flow × extraction ratio × arterial concentration), and inversely dependent on radioactive decay and tissue washout by flow.

$$H_2{}^{15}O_{met.} \propto \frac{(C_a-C_v)}{C_a}\, C_a{}^{*}\, F . \frac{1}{(\lambda+F/V)} \qquad (1)$$

The theoretical relationship between $_2{}^{15}HO_{met.}$ and blood flow for different tissue oxygen extraction ratios is shown in Fig. 1.

At values of perfusion (F/V) which are low, relative to the rate of radioactive decay, the $H_2{}^{15}O_{met.}$ signal has a linear dependence on oxygen extraction and blood flow. However, within the normal range of cerebral blood flow (0·5–0·55 ml./g/minute) the $H_2{}^{15}O_{met.}$ signal is somewhat insensitive to perfusion and linearly dependent on the oxygen extraction ratio. Under these conditions the distribution of radioactivity in the brain principally reflects the distribution of the extraction ratio for oxygen rather than oxygen utilization. The regional extraction ratio is of interest since it represents the balance between the supply and demand for oxygen in the tissues.

In addition to the locally deposited $H_2{}^{15}O_{met.}$ there will be two further principal contributions to the count-rate observed over the head. ^{15}O-labelled red cells will be present, but this component will be relatively small since the vascular volume only constitutes approximately 4 per cent of the parenchymal tissue volume (Phelps *et al.*, 1973). In addition, there will be a significant level of $H_2{}^{15}O$ recirculating to the brain following its production in, and elution from, other body tissues. The 2·1 minute half-life of ^{15}O and the large dilution capacity of the peripheral tissues of the body, will significantly restrict the concentration of $H_2{}^{15}O$ in the recirculating blood relative to that generated in the highly metabolicly active cerebral tissue.

Methods and Results

Animal studies

The relative magnitudes of the secondary cerebral components were determined in monkeys by simulating the respective backgrounds. That due to ^{15}O-labelled red cells can be simulated by breathing $C^{15}O$ which is taken up in the body solely by the red cells. The background due to recirculating $H_2{}^{15}O$ can be simulated by breathing $C^{15}O_2$ since the ^{15}O rapidly exchanges with ^{16}O in blood water (West and Dollery, 1962). For this purpose the monkeys were anaesthetized and paralyzed with Flaxidol to control breathing on a respirator into which the radioactive gases were piped. During the continuous inhalation of $^{15}O_2$, $C^{15}O$ and $C^{15}O_2$, equilibrium count-rates were recorded over the head with a scintillation probe. These were related to the activity in the corresponding arterial blood samples. The contribution to the total head count due to the local production of $H_2{}^{15}O_{met.}$ during $^{15}O_2$ inhalation was extracted by measuring the concentration of ^{15}O on red cells and that of $H_2{}^{15}O$ in the arterial blood and using the appropriate relationships between count-rate over the head and concentration in the blood measured during the inhalations of $C^{15}O$ and $C^{15}O_2$.

In four anaesthetized monkeys 70 per cent of the total count-rate measured over the head was found to be attributable to the locally generated $H_2{}^{15}O_{met.}$ The ^{15}O-labelled red cell component contributed 10 per cent and the remaining 20 per cent resulted from recirculating $H_2{}^{15}O$. The relative strength of the cerebral respiration product $H_2{}^{15}O_{met.}$ was found to be encouraging, especially as the animals were studied under a state of general anaesthesia with probably a lower rate of cerebral metabolism than when conscious. Furthermore, in adult man the body : brain weight ratio will be greater than that for the monkey. Hence the higher peripheral dilution and longer circulation times will result in a lower level of recirculating $H_2{}^{15}O$.

Human studies

We have carried out preliminary studies of the distribution of radioactivity contained within the

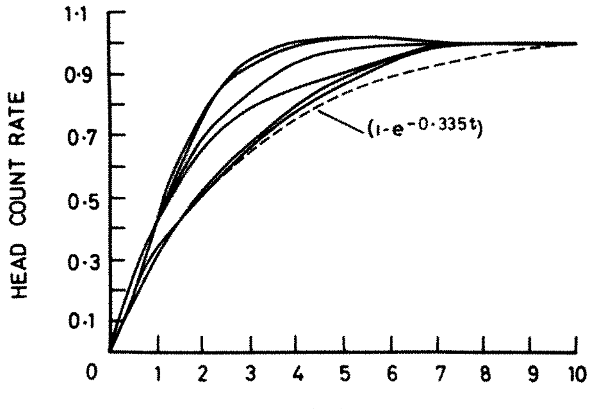

Fig. 2.

Equilibration of radioactivity in the brain of a normal man during the continuous inhalation of ^{15}O. The measurement was repeated on six occasions over a period of four months, the data being normalized to the corresponding ten-minute count-rate.

brain of normal man during the continuous inhalation of $^{15}O_2$. The multicrystal positron camera developed by Burnham and Brownell (1972) was used to view the head while the subject inhaled through a mouthpiece. The radioactive gas was supplied at a rate of approximately half a litre/minute into the room air inlet of a two-way valve. Typically 1 mCi/minute was administered.

Figure 2 shows time activity curves recorded over the head of a normal subject, repeated on six separate occasions over a period of four months. For normalization purposes the data obtained on each occasion have been expressed as a fraction of the corresponding head count recorded after ten minutes of breathing. In general the equilibration times are shorter than would have resulted purely from radioactive decay ($1-e^{-0\cdot335t}$). The combination of blood flow, oxygen consumption and the 2·1 minute half-life of ^{15}O results in equilibrium being reached after six to seven minutes of continuous inhalation. It is of interest to note the variability in the curves which may be attributed to variations in oxygen metabolism or blood flow.

The steady-state distributions of radioactivity in the brain of a normal man while inhaling ^{15}O, $C^{15}O_2$ and $C^{15}O$ are shown in Fig. 3. Each procedure required ten minutes of constant inhalation, the distribution being recorded over the last four minutes. This results in a radiation absorbed dose to the lungs (critical organ) of 0·13 rad per measurement. The distributions obtained during the inhalation of $^{15}O_2$ and $C^{15}O_2$ are striking in that they clearly delineate the brain tissue, whereas that obtained with $C^{15}O$ outlines only the vascular pool. The containment of radioactivity within the vascular shell endorses the fact that functioning cerebral tissue is being observed during ^{15}O-inhalation, with little contribution from the ^{15}O-labelled red cells. The distribution produced during the breathing of $^{15}O_2$ will, due to recirculation of $H_2{}^{15}O$, contain within it a background pattern corresponding to that recorded during $C^{15}O_2$ inhalation. In the absence of the respective arterial activities an accurate subtraction was not possible as in the case of the monkey studies. However, an approximation to this subtraction was made by designating the activity in a section of the scalp to represent the recirculating $H_2{}^{15}O$ present in both the $^{15}O_2$ and $C^{15}O_2$ procedures. This is reasonably justified in that these tissues, by virtue of their relatively low oxygen consumption rate, will have little locally generated water of metabolism laid down in them. It was found, by using this means of monitoring for recirculating $H_2{}^{15}O$, that the subsequent subtraction of the $C^{15}O_2$ distribution from that for $^{15}O_2$ simply enhanced the pattern seen in the raw $^{15}O_2$ data. This normalization, for the series shown, demonstrated that approximately 70 per cent of the total $^{15}O_2$ head count was due to the locally generated $H_2{}^{15}O_{met}$. This figure compares well with the monkey data.

Anterior-posterior views were also recorded during ^{15}O-inhalation. Figure 4 shows the results of focusing the camera in turn on four equally separated vertical planes in the head (Brownell and Burnham, 1972).

During ^{15}O-inhalation, regions with decreased uptake of activity can be seen in the brain. Anatomically these can be related to areas containing white matter and ventricles, which are known to have appreciably less blood flow and rates of oxygen consumption than the surrounding grey matter.

Future extension of the method

During the continuous inhalation of $^{15}O_2$, distinctive patterns of radioactivity are observed in the head which are clearly related to the distribution of functioning cerebral tissue. However, exact interpretation of these data is limited due to dependence on both extraction of oxygen by the tissue and the blood flow (equation (1)). It is possible to cancel out the flow dependence by using the ratio of the $^{15}O_2$ distribution to that obtained while inhaling $C^{15}O_2$ (Fig. 3). This follows since the steady-state $H_2{}^{15}O$ content of the brain produced during the inhalation of $C^{15}O_2$ represents the balance between the arrival of $H_2{}^{15}O$ in the blood (*F.C.*) where *C* is the concentration of $H_2{}^{15}O$ in the arterial blood, and its

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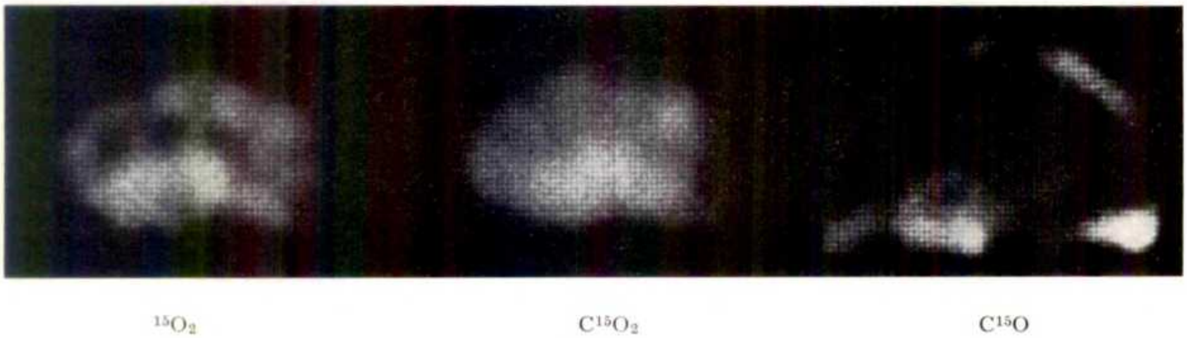

FIG. 3.

Left lateral view of the steady state distribution of radioactivity within the head of a normal subject while continuously inhaling $^{15}O_2$ and $C^{15}O_2$ and $C^{15}O$.

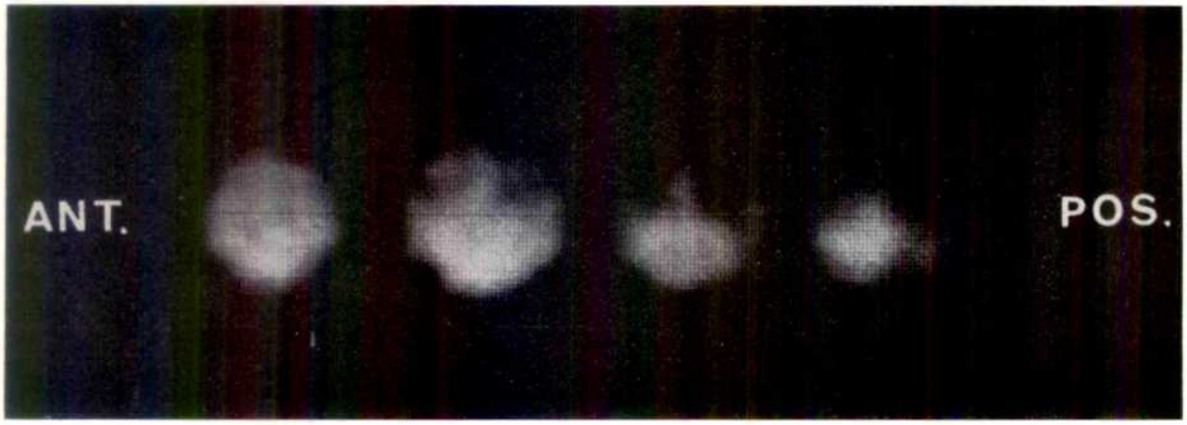

FIG. 4.

Anterior-posterior view of the steady-state distribution of radioactivity in the head of a normal subject while inhaling $^{15}O_2$. The camera data has been focused on four equally spaced vertical planes.

disappearance from the tissue by radioactive decay and flow wash-out (F/V):

$$H_2{}^{15}O \infty \frac{F.C.}{(\lambda+F/V)} \quad . \quad . \quad (2)$$

The ratio of equations (1) to (2) will, since the constant of proportionality is common (geometrical factor), produce a distribution within which the only variable is the oxygen extraction ratio of the tissue:

$$\frac{H_2{}^{15}O_{met.}}{H_2{}^{15}O \text{ from } C^{15}O_2} = \frac{(C_a - C_v).}{C_a} \frac{C_a{}^*}{C} \quad . \quad (3)$$

If the ratio of Ca^* to C is known then absolute regional values for the extraction ratio can be determined.

Equation (2) offers the opportunity to determine regional blood flow provided the geometrical factor is known in addition to regional tissue volume. The radioactive decay of the isotope provides a known perturbation from true equilibration, thus enabling a steady state method to be applied, for measuring blood flow. The necessary *in-vivo* quantitation required in order to apply this principle may be possible by the use of positron–coincidence imaging devices where geometrical factors can easily be determined.

DISCUSSION

The steady-state distribution of radioactivity recorded within the head during the continuous inhalation of $^{15}O_2$ appears to offer a qualitative means for examining regional cerebral function. These functional images of the distribution of oxygen uptake in the brain are theoretically dependent on both regional oxygen extraction and blood flow (equation (1)). The continuous inhalation technique provides a steady state which enables distributions of radioactivity to be measured with good statistical quality using γ-ray imaging devices which are inherently rather insensitive to the 511 keV annihilation radiation. The steady-state method enables tomographic γ-ray emission techniques to be applied, thus improving the contrast in detecting focal defects deep within the brain. Regions of low or zero oxygen uptake will be seen as voids in the equilibrium distribution. In using single passage extraction and clearance techniques, such areas are poorly resolved, since these methods demand that some tracer be partitioned in that region. For clinical application the use of continuous inhalation to give a steady state is attractive in that it is simple, non invasive and enables changes of function to be observed since the ^{15}O-distribution is being continuously replenished.

We have equated the regional signal, recorded during the inhalation of ^{15}O, to the formation of ^{15}O-labelled water of metabolism. The size of this locally generated respiration product when related to the backgrounds due to labelled red cells and recirculating labelled water was found to be encouragingly high in monkeys. This is especially so since these animals have a lower body : brain weight ratio than adult man and were studied under a state of anaesthesia which probably caused some reduction of the locally generated $H_2{}^{15}O_{met.}$ due to lower cerebral metabolism.

During $^{15}O_2$ inhalation in normal man the ^{15}O-labelled red cell component, as assessed by comparison to the $C^{15}O$ measurements, is clearly negligible. The recirculation of $H_2{}^{15}O$ provides a general tissue background which does not dominate the local signal.

Theoretically more definitive measurements of regional oxygen extraction and blood flow could be obtained by this steady-state approach. This would require quantitative measurements of tissue activity relative to those of arterial blood. In addition complementary measurements such as recording cerebral distributions during $C^{15}O_2$ inhalation would be required.

The study of regional cerebral metabolism by a non-invasive method using γ-emitting tracers has proven to be intrinsically difficult. The use of cerebral metabolites such as glucose tagged with ^{11}C is a viable approach. However, the metabolic pathways open to the labelled carbon are so complex as to make count-rates recorded over the head prohibitively difficult to interpret. In this context the use of oxygen utilization as a metabolic index is attractive in that the principal metabolic product is water of metabolism.

The method developed so far does not provide definitive regional measurements of oxygen utilization. However, the numerous attractive features of this method would justify empirical clinical study into its usefulness in understanding focal defects in the brain.

ACKNOWLEDGEMENTS

The support of this work by the Medical Research Council and the Goldsmith Company is acknowledged. Thanks are given for the encouragement of Dr. G. L. Brownell and Dr. M. Welch and the useful discussions of Dr. D. K. Bewley and Dr. J. E. Eichling. The patience of Cyclotron Engineers: Mr. Lee Troutt of the Mallinckrodt Institute and Mr. Bill Bucelevicius of the Massachusetts General Hospital is deeply appreciated.

REFERENCES

BROWNELL, G. L., and BURNHAM, C. A., 1972. M.G.H. positron camera. In *Tomographic Imaging in Nuclear Medicine*, edited by G. S. Freedman, pp. 154–164 (Society of Nuclear Medicine Inc., New York).

BURNHAM, C. A., and BROWNELL, G. L., 1972. A multi-crystal positron camera. *I.E.E.E. Translations of Nuclear Science*, *NS19*, *3*, 201–205.

CARTER, C. C., EICHLING, J. O., DAVIS, D. O., and TER-POGOSSIAN, M. M., 1972. Correlation of regional cerebral blood flow with regional oxygen uptake using ^{15}O method. *Neurology*, *22*, 755–762.

CHESLER, D. A., 1972. Positron tomography and three-dimensional reconstruction technique. In *Tomographic Imaging in Nuclear Medicine*, edited by G. S. Freedman, pp. 176–183 (Society of Nuclear Medicine, New York).

JONES, T., BROWNELL, G. L., and TER-POGOSSIAN, M. M., 1974. "Equilibrium" images of short-lived radiopharmaceuticals for dynamic observations. *Journal of Nuclear Medicine*, *15*, 505.

PHELPS, M. E., GRUBB, R. L., and TER-POGOSSIAN, M. M., 1973. Correlation betwee n Paco^{2} and regional cerebral blood volume by X-ray fluorescence. *Journal of Applied Physiology*, *35*, 741–745.

RAICHLE, M. E., GRUBB, R. L., GADO, M. H., EICHLING, J. O. and TER-POGOSSIAN, M. M., 1975. *In vivo* correlation between regional cerebral blood flow and oxygen utilization in man. In *Blood flow and metabolism in the brain*, pp. 14.3–14.12 (Churchill Livingstone).

TER-POGOSSIAN, M. M., EICHLING, J. O., DAVIS, D. O., and WELCH, M. J., 1970. The measure *in vivo* of regional cerebral oxygen utilization by means of oxyhemoglobin labelled with radioactive oxygen-15. *Journal of Clinical Investigation*, *49*, 381–391.

TER-POGOSSIAN, M. M., DAVIS, D. O., EICHLING, J. O., and CARTER, C. C., 1971. Regional cerebral oxygen metabolism and regional cerebral blood flow compartments measured by means of oxygen-15 in patients with cerebral abnormalities. In *Cerebral Vascular Diseases*, pp. 103–108 (Gune and Stratton Inc.).

TER-POGOSSIAN, M. M., PHELPS, M. E., HOFFMAN, E. J., and MULLANI, N. A., 1975. A positron emission transaxial tomograph for nuclear imaging (Pett). *Radiology*, *114*, 89–98.

WEST, J. B., and DOLLERY, C. T., 1962. Uptake of oxygen-15 labelled CO_2 compared with carbon-11 labelled CO_2 in the lung. *Journal of Applied Physiology*, *17*, 9–13.

1976, *British Journal of Radiology*, *49*, 344–347

A new stannous agent kit for labelling red blood cells with ^{99}Tc^{m} and its clinical application*

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(*Received June, 1975, and in revised form October, 1975*)

ABSTRACT

^{99}Tc^{m} is chosen for labelling erythrocytes for vascular imaging to take advantage of the physical properties of the radionuclide. A new procedure is described which belongs to the category of pre-treatment methods using a kit. Stannous pyrophosphate is the specific reducing reagent. The technique is easier than already published methods: it consists of adding the above reagent to 2 ml. of heparinized blood, waiting five minutes and discarding the serum after centrifugation, then adding the radioactivity required as ^{99}Tc^{m}O$_4$. Labelling yield is superior to 95 per cent.

The influence of technetium concentration of the pertechnetate solution on the labelling yield is evaluated and compensated by a slight adjustment of tin concentration when necessary. *In vitro* and *in vivo* stability studies show that ^{99}Tc^{m}-labelled red cells are suitable for determination of red cell volume, spleen and placental imaging, particularly in emergencies and in paediatrics.

Spleen scanning, placental imaging and determination of red blood cell volume are mostly performed with red cells labelled with ^{51}Cr, or more recently with ^{99}Tc^{m}. The nuclear properties of ^{99}Tc^{m} are ideal for scintigraphy, and give low radiation dose to the patient, thus allowing repeated investigations.

The various techniques proposed for tagging red cells may be classified in three groups according to their labelling yield: Fischer's technique (Fischer *et al.*, 1967) which does not use any reducing agent, the technique of adding reducing agent after the ^{99}Tc^{m} (Eckelman *et al.*, 1971) and the pre-treatment technique where the reducing agent is added before the ^{99}Tc^{m} (Berger and Johannssen, 1969; Nouel and Brunelle, 1970). The last technique gives the highest labelling yield: more than 95 per cent.

The short method we describe belongs to the third group. It uses a new stannous reducing agent, stannous pyrophosphate, which has already been applied (Bardy *et al.*, 1975).

The superiority of stannous pyrophosphate over the commonly-used compounds (stannous chloride or citrate) is due to its chemical stability especially at neutral pH, even at low concentration. To keep this advantage, it must be stored freeze-dried under nitrogen.

As regards red blood cells, the relation between labelling yield and tin content has already been published (Bardy *et al.*, 1975): for very low quantities of reducing reagent (less than 0·1 μg/2 ml. of blood) the yield is poor, whilst in the case of very large quantities (more than 1 μg/2 ml.) three washings of red blood cells are required before the addition of radioactivity to eliminate the excess of tin.

The uptake of tin by the cells is consequently low, less than 0·5 μg/2 ml. of blood. In our experiments, the usual quantity of tin used is 0·3 μg/2 ml. The labelling yield obtained was 96·5 per cent for 95 assays (91–99 per cent).

MATERIALS AND METHODS

In vitro

The reducing reagent was supplied by C.I.S. as TCK-11 kit. The freeze-dried mixture of stannous pyrophosphate, sodium pyrophosphate and sodium chloride was dissolved just before use in 10 ml. of nitrogen-purged saline, which was also supplied in the kit to prevent contamination by oxygen. The solution contained 0·6 μg Sn/ml. The ^{99}Tc^{m}-pertechnetate was obtained from ^{99}Mo/^{99}Tc^{m} generator supplied by C.I.S. or Philips-Duphar. In an additional experiment ^{99}Tc-sodium pertechnetate was added to the radioactive solution to study the effect of carrier on labelling yield and its close relation to red cell tin content.

Blood samples were withdrawn from the patient into heparinized Vacutainer tubes of 5 ml. or into syringes. Centrifugation was performed at 500 *g* for five to ten minutes. Heat alteration of ^{99}Tc^{m}-erythrocytes for spleen imaging was performed in a water-bath at 49·5°C for 20 minutes.

Labelling procedure was as follows: after adding 0·5 ml. of the reducing reagent (0·3 μg Sn) to the heparinized tube containing 2 ml. of the patient's blood, the suspension was gently mixed by hand. Centrifugation was performed 15 minutes later, the supernatant was discarded and the radioactive pertechnetate solution (less than 1 ml.) added to the pre-treated cells. No subsequent centrifugation is necessary for spleen scanning or placental imaging. In the case of blood volume determination, as we will explain in the discussion, centrifugation, separation of supernatant and re-suspension of cells in 1 ml. saline or in the patient's plasma are recommended.

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*Communication presented at the third annual meeting of the British Nuclear Medicine Society, London, March 20–21, 1975.

The data shown in Fig. 1 were obtained by adding 1·2 μg Sn instead of 0·3 μg. The reducing reagent was dissolved for this purpose in 5 ml. saline instead of 10 ml. while 1 ml. of the reducing agent was used for pre-treatment instead of 0·5 ml.

In vivo

Placental imaging was performed five minutes after intravenous injection of 500 μCi of ^{99}Tc-^{m} labelled erythrocytes using a gamma-camera Phogamma III with a low-energy diverging collimator, manufactured by Nuclear Chicago. Spleen scintigraphy was performed 15 minutes after intravenous injection of 1·5 mCi of heat denatured ^{99}Tc^{m}-erythrocytes using a 5 in. diameter crystal and a conventional scintigraph manufactured by SAIP. The dose was reduced to 500 μCi in paediatrics.

Blood volume was measured at times between ten minutes and an hour after intravenous injection of 10 μCi or 100 μCi of erythrocytes labelled with ^{51}Cr or ^{99}Tc^{m} respectively.

RESULTS AND DISCUSSION

Relation between ^{99}Tc carrier and tin content

Figure 1 shows the labelling yield as a function of ^{99}Tc carrier concentration of the radioactive pertechnetate for two values of tin content. The lower value allows a high labelling yield for low concentrations of ^{99}Tc (less than 0·01 μg ^{99}Tc/ml.). The higher value is used when a relatively high ^{99}Tc concentration is present in the radioactive solution (more than 0·03 μg ^{99}Tc/ml.), a concentration which lowers the labelling yield if the lower value of tin content is used.

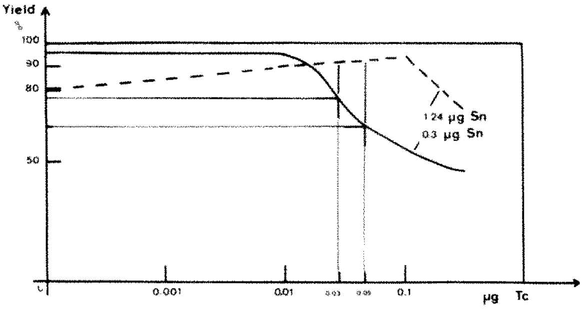

FIG. 1.

Red-cell labelling yield as a function of ^{99}Tc carrier concentration of the pertechnetate solution (μg/ml.), for two concentrations of tin used for pre-treatment of 2 ml. of blood.

TABLE I

Elapsed time between the production date and the calibration date of the generator	First elution performed at the calibration date	
	Volumic activity	Tc concentration
h	mCi	μg/ml.
48	13·2	0·036
72	13·2	0·052
96	13·2	0·075

In order to confirm if a generator eluate may contain per ml. such a quantity of ^{99}Tc carrier, we calculated (Table I), according to the elapsed time between the production date and the calibration date of a 200 mCi ^{99}Mo–^{99}Tc^{m} generator, the technetium concentration (μg/ml.) of the first eluate knowing that 1 Ci ^{99}Mo corresponds to 2·1 μg. The data of Fig. 2 confirm the presence of ^{99}Tc carrier in the first eluate which lowers the activity of red-cell labelling during the preparation of a bolus.

In our case, when the radioactivity to be fixed on erythrocytes is 100 μCi to 1·5 mCi, there is no influence of ^{99}Tc carrier on the labelling yield; nevertheless, we recommend that the first eluate should be discarded for general labelling use.

When one receives daily pertechnetate solutions instead of generators, the ^{99}Tc carrier concentration usually varies from 0·2 to 0·4 μg/25 mCi. More blood (5 ml.) should then be pre-treated, allowing the presence of sufficient tin (1·24 μg) for low activity red-cell labelling.

Stability of labelling

^{99}Tc^{m}-erythrocytes are very stable *in vitro*. Three

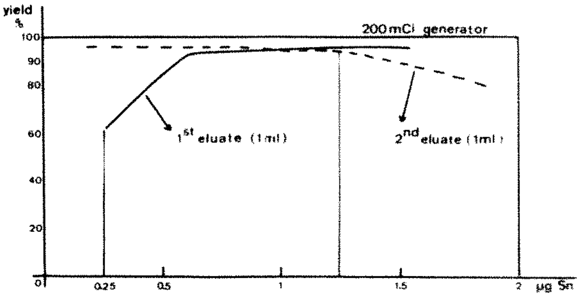

FIG. 2.

Labelling yield as a function of stannous pyrophosphate quantity (expressed as μg tin) and according to the eluate number of a 200 mCi generator.

hours after labelling less than 1·5 per cent of the radioactivity is cleared from the cells.

Comparative determination data of blood volume with ^{51}Cr and ^{99}Tc^{m}-erythrocytes on 20 patients (Fig. 3) do not show any difference at 20 minutes after intravenous injection; however, at one hour the difference reaches 8–10 per cent. This leakage of activity may be reduced to some extent if ^{99}Tc^{m}-erythrocytes are separated from the 3–4 per cent of free radioactivity present just after labelling by centrifuging, discarding the supernatant and resuspending the cells in saline or the patient's plasma. By one hour after injection of ^{99}Tc^{m}-erythrocytes, the leak becomes stabilized.

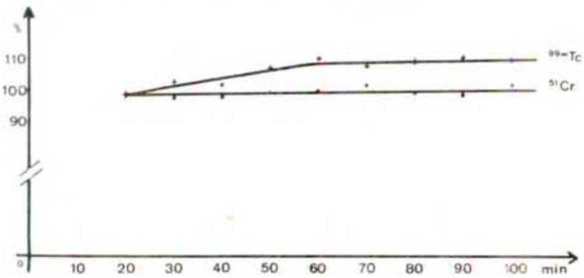

FIG. 3.

Measured blood volume as a function of time after intravenous injection, shown as a per cent of the volume at 10 minutes. Each experimental point represents the average value of 20 determinations.

This leakage may be interpreted as resulting from the fraction of radioactivity bound to cell membrane. Lysis of labelled cells has shown the radioactivity to be in two parts, 95–97 per cent bound to β globin as found by others (Nouel, 1970; Dewanjee, 1974) and 3–5 per cent bound to stroma. This assay corresponds to the progressive appearance of radioactivity in the bladder. The fact that there is no liver radioactivity shows that labelled red cells are not altered by the treatment. G6PD determination and haemolysis studies performed on a few samples have confirmed the integrity of cells after labelling.

This overestimation may be critical for particular haematological studies. Nevertheless, the tracer is

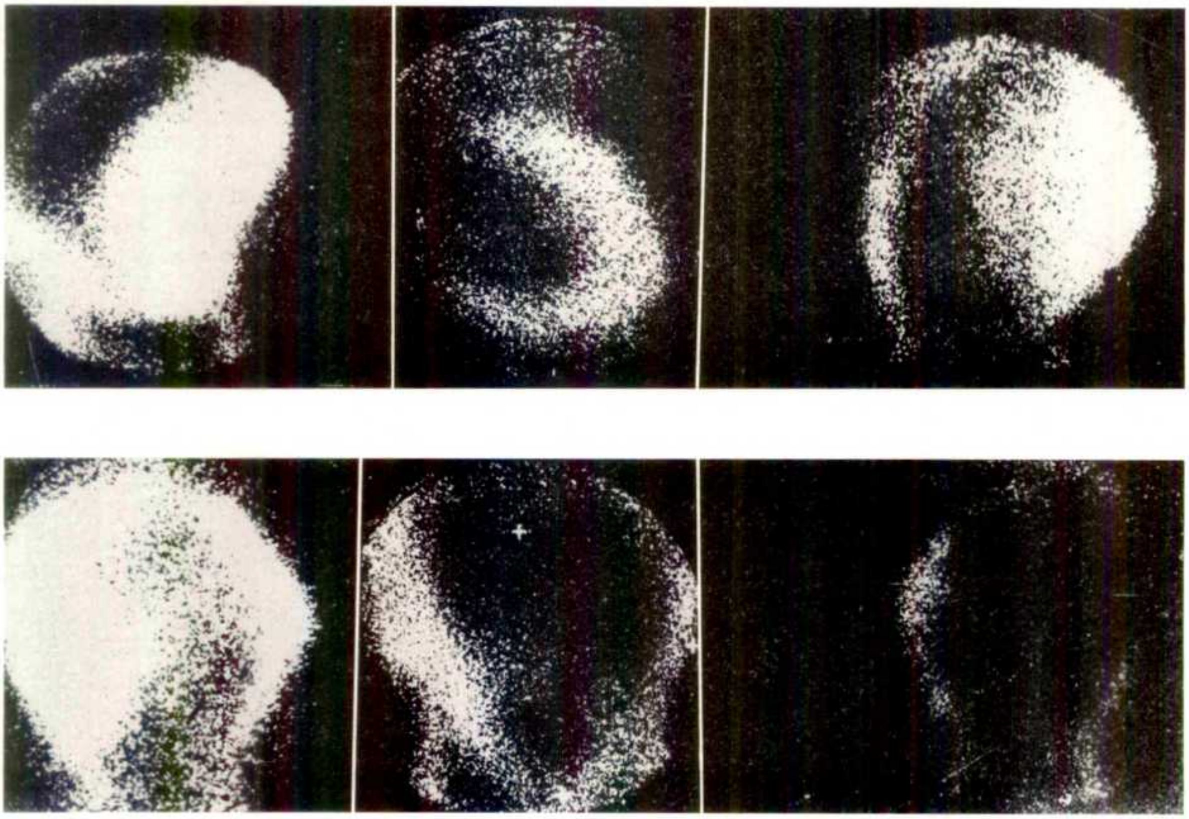

FIG. 4.

Various placental localizations, anterior view. These images were performed 15 minutes after the intravenous injection of 500 μCi of ^{99}Tc^{m}-labelled erythrocytes.

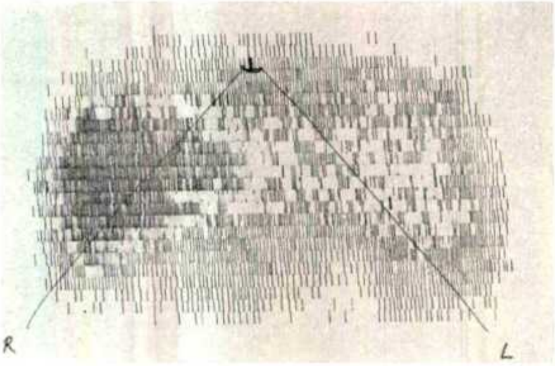

FIG. 5.

Spleen scintigraphy, without any background suppression, (initially coloured), anterior view, from a six-months-old child with a complete "situs inversus", obtained with 500 μCi of ^{99}Tc^{m}-labelled erythrocytes (0·5 ml. total blood).

suitable for emergencies, in paediatrics and when repeated determinations are necessary.

Placental imaging

Forty-five localizations of placenta have been performed, all of good quality (Fig. 4). Due to radioactivity appearing in the bladder at 30 minutes, images are obtained 15 minutes after the intravenous injection.

Spleen scintigraphy

Sixty spleen scintigraphies have been performed, among which three were of infants aged from 6–11 months (Fig. 5). The technique is particularly suitable in these cases as it allows the labelling of 0·5 ml. of the patient's blood.

CONCLUSION

In vitro and *in vivo* studies have shown that erythrocytes labelled with ^{99}Tc^{m} using the described technique are suitable for vascular studies and spleen imaging. The ^{99}Tc^{m} labelling is specially recommended in emergencies, or when frequent blood volume determinations are necessary. Moreover the technique allows the labelling of a very small volume of blood (0·5 ml.) which is particularly useful in paediatrics.

In conclusion, this technique, simple, rapid and reproducible, is recommended for labelling erythrocytes and probably for all figurative blood elements.

REFERENCES

BARDY, A., FOUYE, H., GOBIN, F., BEYDON, J., DE TOVAR, G., and HEGESIPPE, M., 1975. Technetium 99m labelling by means of stannous pyrophosphate: Application to bleomycin and red blood cells. *Journal of Nuclear Medicine*, *16*, 435–437.

BERGER, R., and JOHANNSSEN, B., 1969. Markierung von erythrozyten mit technitium 99m. *Wissenschaftliche Zeitschrift der Karl-Marx-Universität Leipzig. Mathematisch-Naturwissenschaftliche Reihe*, *18*, 635–638.

DEWANJEE, M. K., 1974. Binding of ^{99m}Tc ion to hemoglobin. *Journal of Nuclear Medicine*, *15*, 703–706.

ECKELMAN, W., RICHARDS, P., HAUSER, W., and ATKINS, H., 1971. Technetium labeled red blood cells. *Journal of Nuclear Medicine*, *12*, 22–24.

FISCHER, J., WOLF, R., and LEON, A., 1967. Technetium 99m as a label for erythrocytes. *Journal of Nuclear Medicine*, *8*, 229–232.

NOUEL, J. P., and BRUNELLE, P., 1970. Le marquage des hématies par le technetium 99m. Son intérêt clinique. *La Presse Médicale*, *78*, 73–74.

Book review

Recent Results in Cancer Research. Gliomas. Edited by J. Hekmatpanah, pp. 164, 1975 (Berlin, Heidelberg, New York, Springer-Verlag,), $23.30.

This book is a report of the proceedings of a symposium on cerebral gliomas held at the University of California in May 1974, and is published in the series *Recent results in Cancer Research*.

The 14 papers by various experts in this field cover modern concepts of experimental tumour production both *in vitro* and *in vivo*, the diagnosis of human gliomas by neuroradiology, including the use of the EMI scanner and proton radiography, and their treatment by surgery, radiotherapy and chemotherapy.

The main conclusion to be gained from the symposium is that in spite of advances in knowledge of tumour biology and improvements in modern diagnostic methods, the prognosis for patients with malignant gliomas remains very poor. However, a more hopeful note is struck by Chang in a paper outlining some new radiotherapeutic approaches. He describes the search for more effective régimes of dose fractionation and the use of high-LET radiations and radiosensitizers including hyperbaric oxygen, electron-affinic drugs, hyperthermia and hypermetabolic states. To date, not one of these methods has proved effective, but it would seem possible that a combination of these modalities may prove successful in the future.

Although this book will be a most useful asset to the library of any department pursuing either research into or treatment of gliomas, it is too specialized for the more general reader.

THELMA D. BATES.

1976, *British Journal of Radiology*, *49*, 348-350

^{125}Iodinated fibrinogen uptake in inflammatory joint disease as a complicating factor in the detection of deep vein thrombosis

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(*Received June, 1975*)

Abstract

An enhanced uptake of ^{125}I-fibrinogen observed in the arthritic knee joint of a patient suspected of deep vein thrombosis was confirmed in a number of patients with inflammatory joint disease in the absence of thrombosis.

Whilst this is a potentially serious source of false positive diagnoses, the possibility also exists that this phenomenon could be used to evaluate the degree to which active disease is present in the joints of patients suffering from inflammatory disease.

The use of the fibrinogen uptake test, using fibrinogen labelled with either ^{125}I or ^{131}I, has proved to be a useful means of detecting newly formed deep vein thrombosis (Negus *et al.*, 1968; Kakkar *et al.*, 1970; Maas *et al.*, 1971; Kakkar, 1972). Labelled fibrinogen will tend to accumulate wherever fibrin deposition is occurring and this has been utilized to evaluate renal transplant rejection (Salaman, 1972). Hobbs (1962) observed fibrinogen uptake in a variety of conditions in experimental animals including wound healing and ethanolamine induced inflammation where a transitory accumulation of fibrinogen was observed.

During the routine clinical screening for thrombosis of an arthritic patient we observed a significant non-transitory uptake of ^{125}I fibrinogen in a knee joint with an active arthritis. This phenomenon was observed in a number of other cases.

Clinical Method

Each patient received 100 μCi ^{125}I fibrinogen (Amersham) intravenously. The activity present in the thyroid, heart and legs was measured periodically, up to 96 hours post-injection, by means of a scintillation detector. The detector was placed over the patient so that the detection field was 14 × 14 cm. Each leg was measured from top to bottom and depending on length five or six separate regions were examined. The measurements obtained were expressed as a ratio: region activity/heart activity. Prior to and for three weeks following the administration of ^{125}I fibrinogen the patient was treated with orally administered iodine solution to minimize uptake of free ^{125}I in the thyroid.

Clinical Observations

Case 1

An adult female patient with no evidence of active inflammatory joint disease or of deep vein thrombosis of the lower limbs. The distribution of activity in the lower limbs 72 and 96 hours post injection is shown in Fig. 1. The distribution pattern remains constant in both limbs showing a slight overall decrease in activity with time.

Case 2

An adult male similar to Case 1. The distribution of activity in the lower limbs 72 and 96 hours post injection is

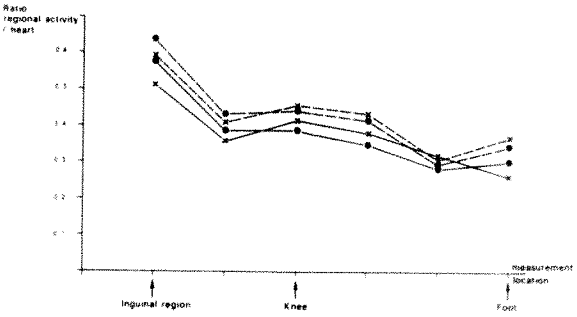

FIG. 1.

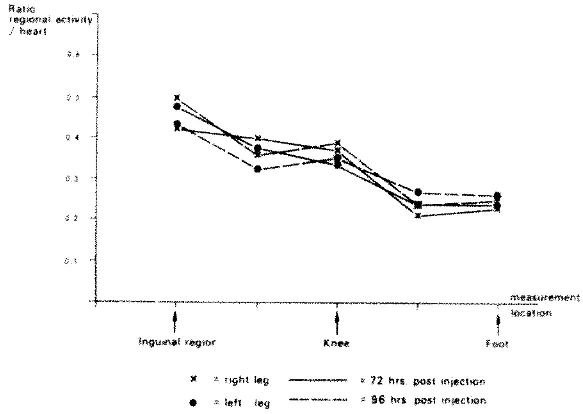

FIG. 2.

FIGS. 1 AND 2. Normal distribution patterns of ^{125}I fibrinogen in the lower limbs 72 × 96 hours post-injection.

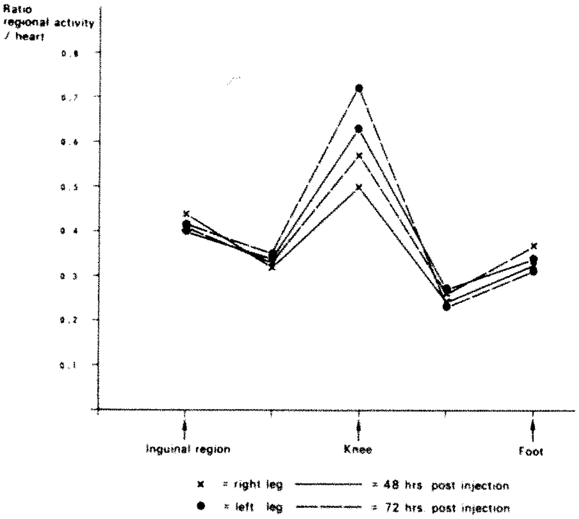

FIG. 3.

^{125}I fibrinogen distribution in the lower limbs of a female patient with rheumatic disease in both knees 48 × 72 hours post-injection.

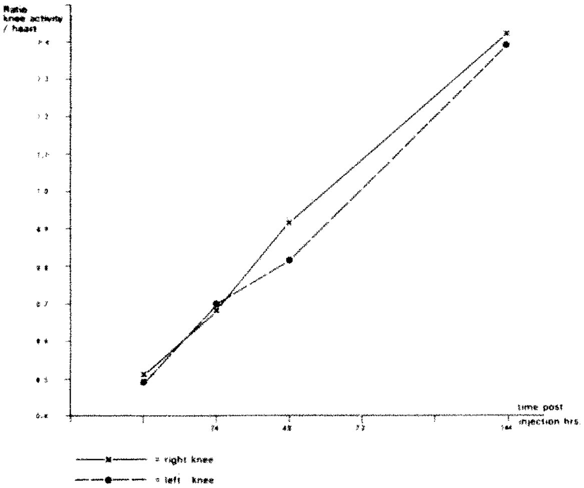

FIG. 4.

^{125}I fibrinogen activity distribution in the knee joints of a patient with active rheumatic disease in both knees.

shown in Fig. 2. Both of these patients show normal distribution patterns similar to those reported from studies of large groups of patients (Maas, 1974).

Case 3

This was a female patient with active rheumatic disease in both knee joints. The ^{125}I fibrinogen distribution patterns in the lower limbs 48 and 72 hours post injection are shown in Fig. 3. A significant uptake in both knees can be observed, which appears to increase with time.

Case 4

Also a female patient similar to Case 3. Measurements above the knee joints show a significant increase in fibrinogen uptake with relation to time (Fig. 4).

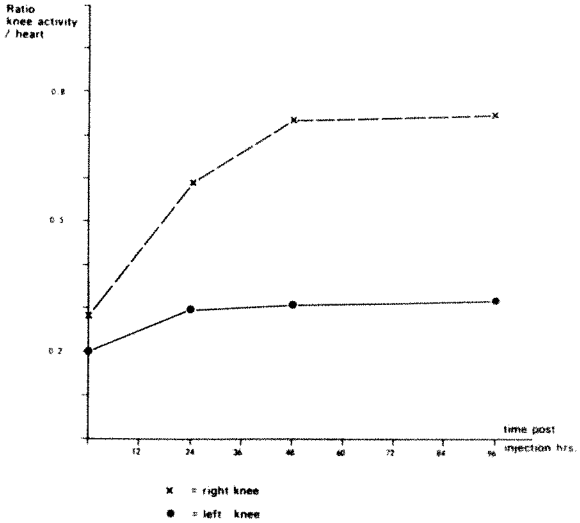

FIG. 5.

A similar patient to Fig. 4, but with a quiescent left knee.

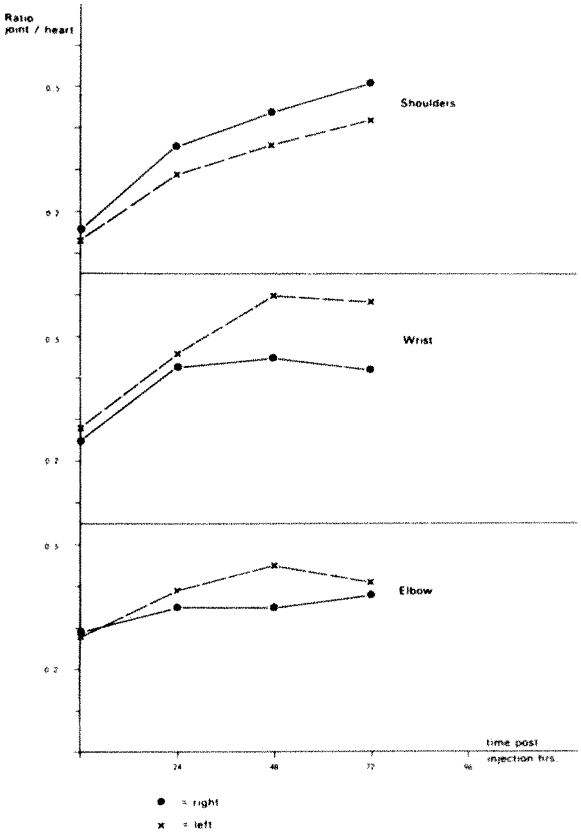

FIG. 6.

^{125}I fibrinogen distribution in various joints of a rheumatic patient with generalized active disease.

Case 5

This female patient was of some interest because she presented a quiescent rheumatic left knee and a right knee with active inflammatory joint disease. The ^{125}I fibrinogen distribution in both knees in relation to time is shown in Fig. 5. In Fig. 6 the ^{125}I fibrinogen distribution in various joints of a patient with generally active rheumatic disease is shown in relation to time. An accumulation of fibrinogen can be observed in the joints with active disease.

Discussion and Conclusions

None of the cases discussed in this report were suspected to be suffering from thromboembolytic disease and there was no evidence of it. On the basis of these results it is evident that the presence of inflammatory joint disease can be a significant source of false positive results when fibrinogen is used to detect thrombosis. This could also be the case when the biological half life of fibrinogen in blood is measured as a systemic test for thrombosis. Measurements of this parameter in the cases reported in this study confirmed this. In patients with active uptake of fibrinogen in joints a faster biological half life in blood was observed similar to that reported for thrombosis.

It would appear that there is a possible relationship between the rate of fibrinogen uptake and the state of activity of the inflammatory joint disease which could be useful for diagnosing and evaluating therapy. Further studies will be required to confirm this.

REFERENCES

Hobbs, J. T., 1962. External measurement of Fibrinogen uptake in experimental venous thrombosis and other local pathological states. *British Journal of Experimental Pathology*, *43*, 48–58.

Kakkar, V. V., Nicolaides, A. N., Renney, J. T. N., Friend, J. R., and Clarke, M. B., 1970. ^{125}I-labelled fibrinogen test adapted for routine screening for deep vein thrombosis. *Lancet*, *1*, 540–542.

Kakkar, V. V., 1972. Isotopic detection of deep venous thrombosis. II. Prevention and diagnosis. In *Thromboembolism: Diagnosis and Treatment* (Kakkar, V. V. and Jouhar, A. J.), pp. 101. (Churchill Livingstone, Edinburgh and London).

Maas, A. P. C. van der, Teulings, F. A. G., and Ottolander, G. J. H. den, 1971. The use of labelled fibrinogen in the diagnosis of venous thrombosis. *Thrombosis et diathesis haemorrhagica*, *26*, 1–8.

Maas, A. P. C. van der, 1974. ^{131}I-fibrinogen. Clinical study in normals and in patients with venous thrombosis. Ph.D. dissertation. University of Utrecht.

Negus, D., Pinto, D. J., Lequesne, L. P., Brown, N., and Chapman, M., 1968. ^{125}I-labelled fibrinogen in the diagnosis of deep-vein thrombosis and its correlation with phlebography. *British Journal of Surgery*, *55*, 845–839.

Salaman, J. R., 1972. Renal transplant rejection detected with ^{125}-fibrinogen. *Proceedings Royal Society of Medicine*, *65*, 476.

Book review

The Radiology of Joint Diseases. By Vassil Tzonchev, Kurt Seidel, Michael Dimitrov, and Klaus Herrmann, pp. 221, 353 illus., 1973 (translated by Klaus Herrmann), (London, Butterworth and Company), £14·00.

This book has been produced through the collaboration of a team of rheumatologists and radiologists from the People's Republic of Bulgaria and the German Democratic Republic. The authors obviously write from a considerable experience and deep understanding of the problems in diagnosis of the commoner arthropathies. The book is mainly devoted to a large series of radiographs, each of which is carefully annotated. Particular emphasis has been placed on the illustration of chronic forms of rheumatic polyarthritis and degenerative joint disease.

Although the book is primarily intended as a radiographic atlas of common joint disorders for clinicians, I feel that there are some aspects of presentation which require comment from a radiologist's viewpoint. The introductory and illustrative sections of the book are quite separate. Therefore, the absence of figure numbers from the text is obtrusive if frequent reference is made from one part to the other. In some instances, a definitive diagnosis is not given with the illustration, even though this would appear to show characteristic radiographic features. For example, in Fig. 12, the diagnosis of Forestier's flowing spinal hyperostosis could be offered in the lumbar spine of a 73-year-old man suffering from diabetes mellitus. The hip joints of a 27-year-old woman suffering systemic lupus erythematosis are illustrated in Figs. 216 and 217. Radiological signs are evident which should alert the clinician to the possibility of complicating femoral head necrosis.

The original text has been entirely translated into English by one of the authors. This Herculean task has been performed with enviable skill. Occasionally, however, the unfortunate transposition of such words as pseudo-plastic, septical, hypo-alimentation and panaritium, leaves the reader in some doubt about the intended meaning.

I personally feel that some of these aspects of presentation will detract from the value of this book to a radiological readership.

W. M. Park.

1976, *British Journal of Radiology*, *49*, 351–356 APRIL 1976

Method of constructing a dose-response curve for normal cells *in situ**

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(Received March, 1975 and in revised form September, 1975)

ABSTRACT

A method is presented for planning experiments and analysing data with a view to determining in detail the shape of a single-dose survival curve for normal cells exposed *in situ* to relatively low doses of radiation. Applying this method to data published on the responses of gastric mucosal and colonic stem cells showed that the single-dose survival curves for these cells were linear up to about 250 rads, after which they bent downwards. Some applications of this method are discussed.

It would be of value to radiobiologists and radiotherapists if the response of normal cells *in situ* to relatively low doses of radiation could be measured accurately. Most assay systems require relatively high doses, and it is difficult to determine the low-dose response of normal cells *in situ* (Withers, 1975).

In this paper, a method for planning experiments and analysing data to show details of the initial region of a dose-response curve will be presented.

THEORY

The basic idea is that, although damage from low doses can be detected neither by assays of colony-forming ability *in situ* nor by arbitrary scales of tissue reaction, repeated low doses do lead to detectable damage amenable to quantitation.

Our method requires three assumptions:

(1) A given amount of damage, scored by an arbitrary scale or a given number of colonies, corresponds to a particular level of cell depletion in the target cell population, whatever irradiation schedule is used to obtain it.

(2) Target cells do not multiply between the first and last exposure.

(3) The shape of the survival curve at the end of each fraction interval is precisely the same as the shape of the single exposure curve starting from zero dose.

On the basis of these assumptions, it is possible to plot the response of cells to each dose fraction and a single-dose response curve may be constructed using data from a variety of multifraction régimes, because if the total dose required to produce a given level of damage in n_1 equal fractions is Dn_1, the damage from each fraction $\frac{Dn_1}{n_1}$ is $\frac{1}{n_1}$ of the final injury assayed.

However, the single-dose curve derived in this way from multifraction experiments, using an arbitrary scale of injury, does not give the detailed shape of the curve. Ideally, we need to know the tangent to the curve at a given dose. Since this is not possible using such data, we must use the slope of a line passing through two points as close to each other as possible on the dose-survival curve.

The line which passes through two arbitrarily chosen points on a single-dose response curve will be characterized by two parameters: the intercept dose, D_{m}, with the abscissa of the extrapolated part of this line, and D_{h}, the inverse of the slope of this line. Therefore, the relationship between pairs of closely spaced doses and the values of D_{m} and D_{h} can define the detail of a single-dose survival curve. Values for D_{m} and D_{h} will be calculated as follows:

Figure 1 shows two model dose-response curves for multiple equal dose fractions. The vertical axis represents the level of damage on a linear scale or surviving fraction on a logarithmic scale. An arbitrarily chosen level of damage produced by each régime of multiple equal dose fractions is shown as 1. Because the triangles ACG and ABD are similar, the D_{m} value of a line passing through two points on a curve can be determined as follows (see Fig. 1):

$$\frac{D_{\mathrm{n1}}/n_1 - D_{\mathrm{m}}}{1/n_1} = \frac{D_{\mathrm{n2}}/n_2 - D_{\mathrm{m}}}{1/n_2}$$

$$D_{\mathrm{n1}} - n_1 D_{\mathrm{m}} = D_{\mathrm{n2}} - n_2 D_{\mathrm{m}},$$

$$\text{Hence, } D_{\mathrm{m}} = \frac{D_{\mathrm{n2}} - D_{\mathrm{n1}}}{n_2 - n_1}$$

where D_{n1} and D_{n2} are the total doses necessary to

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*This investigation was supported by NIH Research Grant Numbers CA-06294 and CA-11138 from the National Cancer Institute.

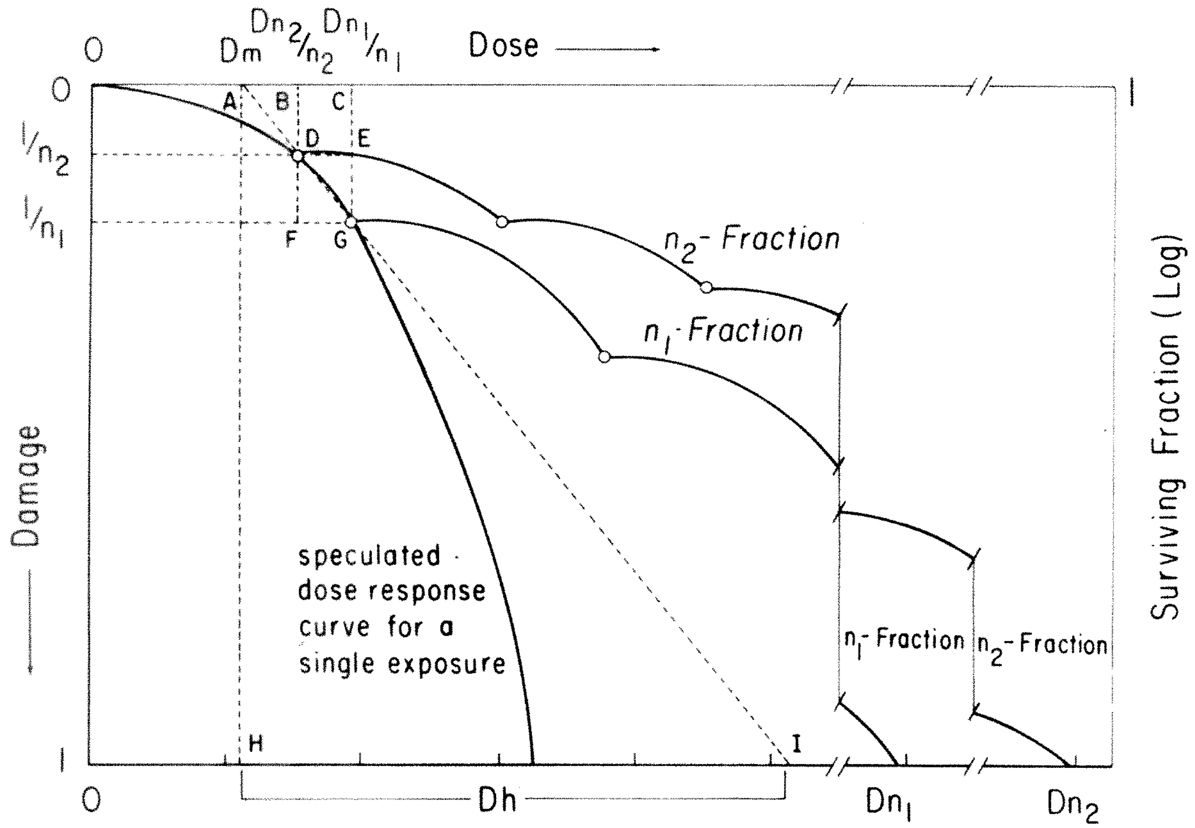

Fig. 1.

Model survival curves for multiple dose fractions. The bending curve is the single-dose survival curve. The upper solid line is the "effective" survival curve for n_2 equal fractions: the lower curve is for n_1 equal fractions. The total doses for an effect (denoted as 1) are Dn_2 given as n_2 fractions and Dn_1 given as n_1 fractions. D_m is the intercept with the zero-effect abscissa that results from extrapolating the segment D–G of the single-dose curve. D_h is a dose inversely related to the slope of the curve between D and G.

produce a given level of damage (isoeffect dose) in n_1 and n_2 equal fractions, respectively.

This value, D_m, is precisely equal to the D_q value defined by Alper *et al.* (1962), if a dose-response curve of normal cells *in situ* is of the so-called C-type, and if these two points are in the exponential region of the curve. The value of D_m is also an average total dose increment per increased number of fractions required for an iso-effect when the number of fractions is increased from n_1 to n_2.

As the triangles AHI and DFG in Fig. 1 are similar, the value of D_h can be determined as follows:

$$D_h/1=\left(\frac{D_{n1}}{n_1}-\frac{D_{n2}}{n_2}\right)\Big/\left(\frac{1}{n_1}-\frac{1}{n_2}\right),\text{ hence,}$$

$$D_h=\frac{n_2D_{n1}-n_1D_{n2}}{n_2-n_1}$$

The value of D_h is directly proportional to D_0 only if the two points are in the exponential region of a C-type dose-response curve.

The value of D_m is calculated from pairs of isoeffect doses, using any level of injury. A series of D_m values derived from various multifraction exposures may then be plotted as a function of dose per fraction. The resulting relationship between pairs of doses per fraction (for an isoeffect) and the corresponding D_m value gives an indication of the shape of the survival curve.

On the other hand, the value of D_h is the dose necessary to produce a given level of damage, and therefore depends on the level of damage chosen as the isoeffect.

If a dose-response curve is continuously downward bending, the value of D_m would increase and that for D_h would decrease with increasing dose per fraction (see Fig. 2A). However, if the curve becomes

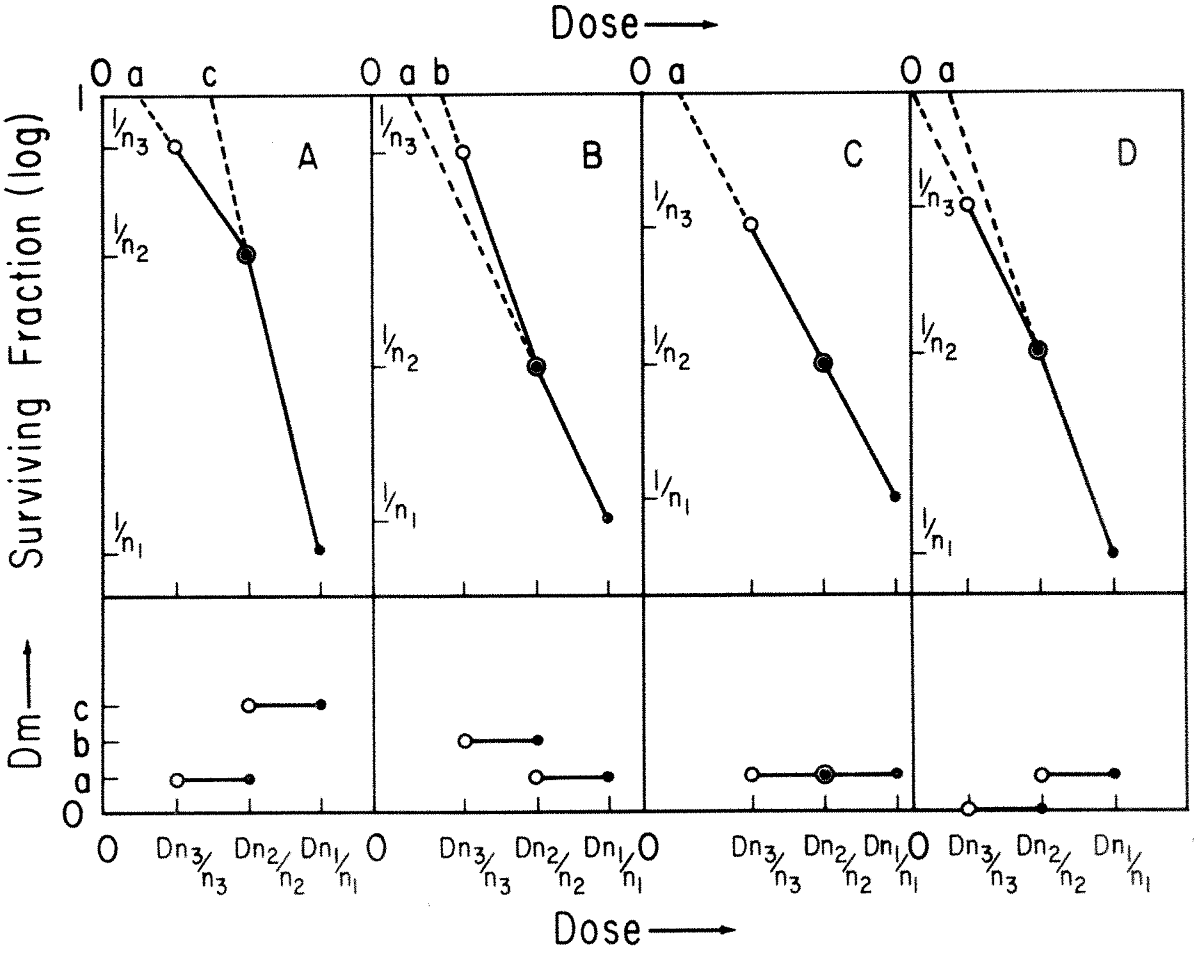

FIG. 2.

Diagrammatic representation of the relationships between the shape of a dose-response curve for single exposure and values of D_m determined from isoeffect doses obtained from multifraction exposures. Open and closed circles indicate, respectively, smaller and larger doses of a pair of isoeffect doses per fraction used to calculate D_m.

exponential, and the doses per fraction for an isoeffect are large enough to reduce survival to the exponential region, then the value of D_m and D_h would be constant (Fig. 2C). If the initial part of a curve is exponential, the value of D_m would be zero as long as the larger of the pair of doses per fraction remains within this exponential region (Fig. 2D). When the slope of a curve becomes less steep, the value of D_m decreases while the D_h value increases with an increase in dose per fraction (Fig. 2B).

Therefore, by determining (from pairs of multifraction dose-response curves) values for D_m and D_h at a certain isoeffect, it is possible to reconstruct the shape of the single dose-response curve.

APPLICATION TO PUBLISHED DATA

Chen and Withers (1972) published multifraction dose-response curves for the stem cells of gastric mucosa exposed to γ rays, using loss of colony-forming ability as an end point. The time interval between doses was 24 hours. Repair of sublethal damage seemed to be complete eight hours after a dose of 700 rad and cell division began 24 hours after the first dose. Therefore, it can be said that the data reported were obtained in conditions satisfying the assumption necessary to apply the D_m and D_h concept, except that with larger numbers of dose fractions, repopulation by surviving cells between doses probably occurred.

TABLE I

Total doses (rad) necessary to produce an average survival of 40 cells per circumference for gastric mucosa crypt cells of mice, and D_m and D_h values

Number of fractions	Total dose	Dose per fraction	$D_{n2}-D_{n1}$	$n_2D_{n1}-n_1D_{n2}$	n_2-n_1	D_m	D_h
1	1,500	1,500					
			1,970–1,500	3,000–1,970	2–1	470	1,030
2	1,970	985					
			2,360–1,970	5,910–4,720	3–2	390	1,190
3	2,360	787					
			2,920–2,360	11,800–8,760	5–3	280	1,520
5	2,920	584					
			4,270–2,920	29,200–21,350	10–5	270	1,570
10	4,270	427					

Isoeffect doses quoted from the paper by Chen and Withers (1972).

The various multifraction doses required to reduce stem-cell survival to 100, 40, 10, 4 and 1 cell(s) per circumference were chosen arbitrarily for determining D_m values. Table I shows the total doses required to achieve an average survival of 40 cells per circumference, and the calculated D_m and D_h values. For example, the isoeffect doses for single and two-equal fractions are 1,500 and 1,970 rad, respectively, and the value for D_m and D_h are 470 and 1,030 rad, respectively. From the standpoint of a single-dose response curve, these values of D_m and D_h of the line passing through points at 1,500 rad and 985 rad on a curve are 470 and 1,030 rad, respectively. The relationship between doses per fraction and D_m and D_h values is illustrated inFig. 3. D_h values decrease with increase in dose per fraction. D_m values increase with increase in dose per fraction, but there are two steps within the dose ranges reported. The first step occurs at a D_m value of 300 rad, which is found when doses per fraction range from 500 to 1,000 rad. The second step is at a D_m value of 500 rad, that is, at doses per fraction of 1,000 to 1,700 rad. This implies, as illustrated in Fig. 2, that the single-dose response curve for stem cells of gastric mucosa bends downward, but that it has at least two linear (exponential) portions, one between 500 and 1,000 rad, and the other between 1,000 and 1,700 rad. The shape of the dose-response curve at doses less than 400 rad cannot be determined due to lack of data.

Figure 4 presents, as a function of dose per fraction, D_m and D_h values for epithelial cells of murine colon (Withers and Mason, 1974). In these experiments, the interval between fractions was three hours, sufficient for essentially complete recovery from sublethal injury. All of the data quoted were assumed to satisfy the necessary conditions for calculating D_m and D_h values. For calculating D_m values, total doses required to achieve arbitrarily chosen survival levels of 50, 10 and 5 cells per circumference were used. The D_h values were determined for a level of survival of ten cells per circumference.

Figure 4 shows that D_m increases and D_h decreases with increase in dose per fraction. This suggests that the dose-response curve is continuously bending downward. There appears to be one step in the relationship between dose per fraction and the value of D_m within the dose ranges examined: the D_m value remains constant at 200 rad for doses per fraction of 600 to 900 rad.

As discussed previously, if the survival curve is initially exponential, the value of D_m will be zero as long as the larger of a pair of doses per fraction used to determine D_m is within the limits of the exponential region. Conversely, if the D_m value is zero, the survival curve is exponential to ***at least*** the larger of the two isoeffect doses used to calculate D_m. In Fig. 4, D_m is zero at doses per fraction less than 250 rad. The data in Fig. 4 imply that the single-dose survival curve for colonic epithelial cells of the mouse is exponential up to 250 rad, followed by a downward bending curve that becomes linear over the dose range 600–900 rad and then begins bending downward again.

Discussion

There has been no good experimental method for determining the response of normal cells *in situ* to relatively low doses of radiation. The method described in this paper may be used to estimate the effects of low doses of radiation on normal cells *in situ* using data from multifraction experiments. Provided certain conditions are met, this method can

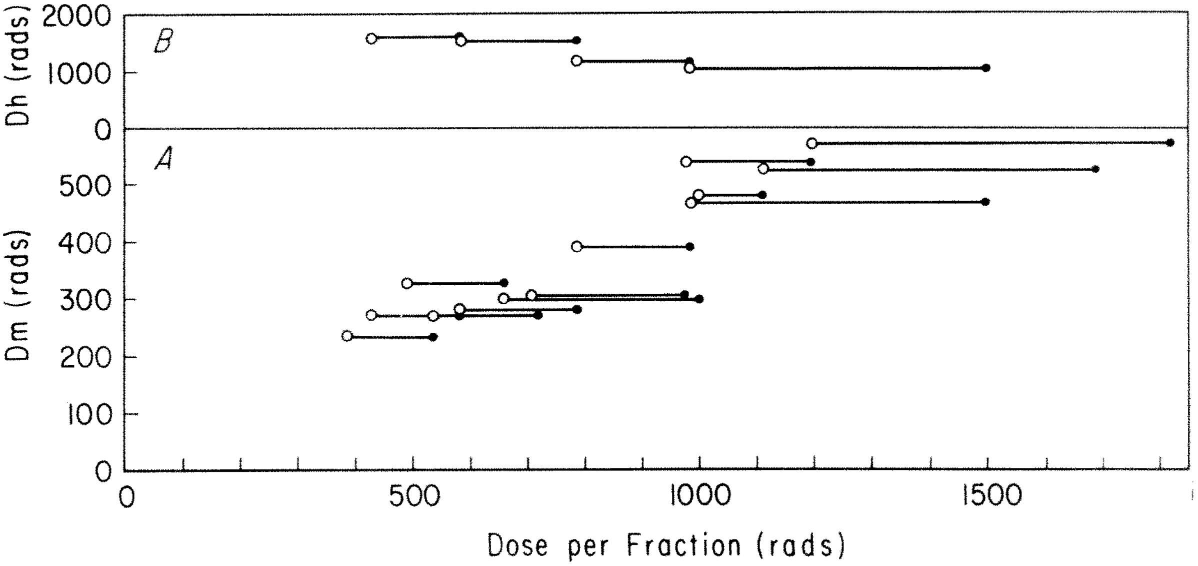

Fig. 3.

D_m (A) and D_h (B) values of the dose-response curve of stem cells of gastric mucosa (Chen and Withers, 1972) as a function of doses per fraction. Open and closed circles correspond to smaller and larger doses per fraction used in calculating D_m and D_h, as shown in Fig. 2. Calculation of D_h was based on doses needed for an isoeffect of 40 surviving cells per circumference.

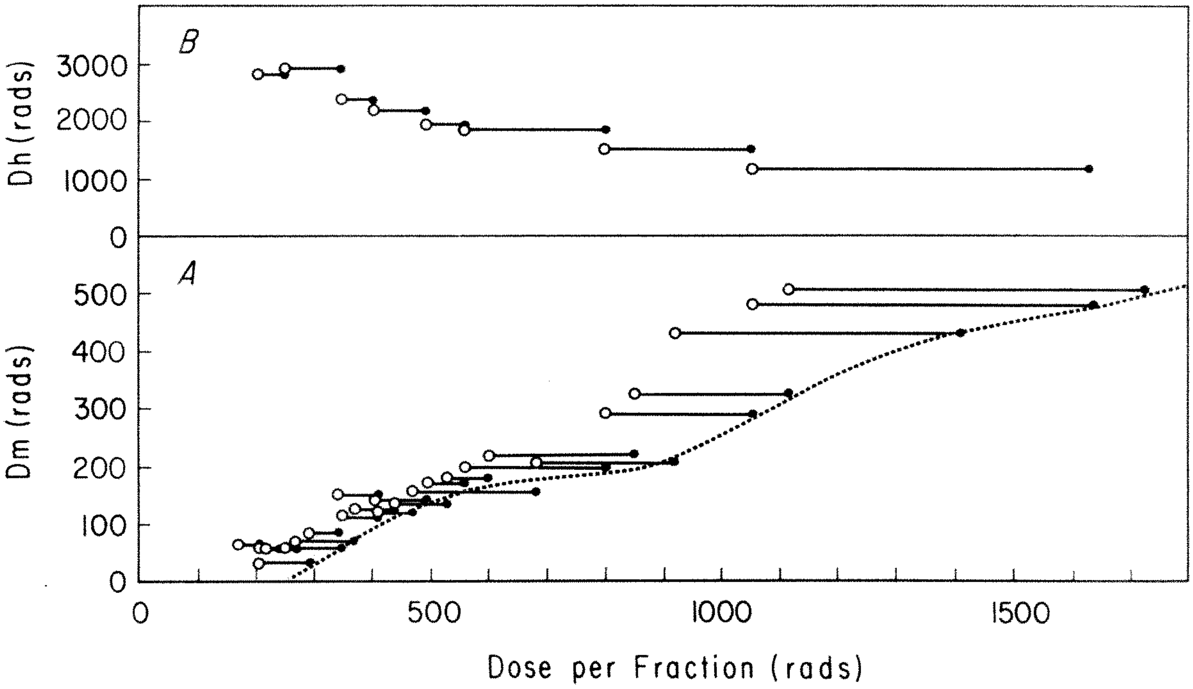

Fig. 4.

D_m (A) and D_h (B) values for the dose-response curve of stem cells of colonic epithelium (Withers and Mason, 1974) as a function of doses per fraction. Open and closed circles have the same meaning as in Figs. 2 and 3. Calculation of D_h was based on doses required for an average survival level of ten cells per circumference.

be used in analysing the responses of a wide variety of tissues using various end points, *e.g.* loss of colony-forming ability, desquammation of skin, etc. If it can be assumed that a given level of reaction corresponds to a particular level of target cell depletion regardless of the irradiation schedule used to achieve it, then the degree of damage chosen as an isoeffect does not affect the conclusions drawn from the relationship between doses per fraction and the values of D_m and D_h.

Since two points, $\left(\frac{D_{n1}}{n_1}, \frac{1}{n_1}\right)$ and $\left(\frac{D_{n2}}{n_2}, \frac{1}{n_2}\right)$, define a portion of a single-dose response curve, the closer the two points, the more accurately the nature of a single-dose response curve can be estimated. Therefore, the number of fractions n_1 and n_2 should be selected so that n_2-n_1 will be as small as possible. The interval between doses, depending upon the kinds of cells and other physiological conditions that may affect the radiosensitivity of cells, must be chosen to satisfy the conditions prescribed.

Fowler *et al.* (1974) constructed a dose-response curve for skin reaction using data from multifractionated exposures. Their method is very simple and reasonably accurate, assuming that an equal amount of damage is caused by each fraction in multifractionated exposures. The formulae presented in this paper are derived from basically the same idea as theirs, but their method shows only the form of dose response curve and does not permit as detailed an analysis as the D_m, D_h concept outlined here.

Dutreix, Wambersie and Bounik (1973) determined the dose increment (D_r) per pair of fractions required for an isoeffect in normal tissue when the number of fractions ($N \times D_s$) are replaced by 2N fractions ($2N \times D_i$ or $N \times 2D_i$); then $D_r = 2D_i - D_s$. D_r is a special form of D_m: when $n_2 = 2 \times n_1$, D_s is equal to D_m. In other words, D_m is a general form of D_r. In their formula, n_2 must be equal to $2 \times n_1$, but using D_m, any number of fractions may be used in multifraction experiments.

Withers (1975) proposed the following as a general formula for the incremental dose per fraction determined in experiments of the type reported by Dutreix *et al.*:

$$\Delta D_r = \frac{\Sigma D_i - \Sigma D_s}{n_i}$$

where ΔD_r is the dose increment for each of n_i fractions when the number of fractions is increased from n_s to n_i. A value of zero for ΔD_r gives an estimate of D_f, the point of flexure between an initial exponential region and a bending region of a survival curve, if an exponential region exists. However, the same information can be obtained from measurements of D_m which has the advantage of describing in more detail the shape of the single-dose survival curve at relatively lower doses.

Furthermore, not only the end point chosen, but also the number of fractions, n_s, affects the value of ΔD_r, whereas the relationship between doses per fraction and the value of D_m is independent of both the end point used and the number of fractions. Thus, the D_m and D_h concept is superior in showing the nature of a dose-response curve over a wider dose range.

REFERENCES

ALPER, T., FOWLER, J. F., MORGAN, R. L., VONBERG, D. D., ELLIS, F., and OLIVER, R., 1962. The characterization of the type C survival curve. *British Journal of Radiology*, *35*, 722–723.

CHEN, K. Y., and WITHERS, H. R., 1972. Survival characteristics of stem cells of gastric mucosa exposed to localized gamma irradiation in C3H mice. *International Journal of Radiation Biology*, *21*, 521–534.

DUTREIX, J., WAMBERSIE, A., and BOUNIK, C., 1973. Cellular recovery in human skin reaction: Application to dose fraction number overall time relationship in radiotherapy. *European Journal of Cancer*, *9*, 159–167.

FOWLER, J. F., DENEKAMP, J., DELAPEYRE, C., HARRIS, S. R., and SHELDON, P. W., 1974. Skin reactions in mice after multifraction X-irradiation. *International Journal of Radiation Biology*, *25*, 213–223.

WITHERS, H. R., and MASON, K. A., 1974. The kinetics of recovery in irradiated colonic mucosa of the mouse. *Cancer*, *34*, 896–903.

WITHERS, H. R., 1976. Response of various tissues to low doses of γ-radiation. In *Current Topics in Radiation Research*, eds. M. Ebert and A. Howard, (North Holland Publishing Co., Amsterdam) (in press).

1976, *British Journal of Radiology*, *49*, 357–359 APRIL 1976

Recovery in mammalian cells irradiated with a beam of π⁻-mesons

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(*Received July, 1975*)

ABSTRACT

HeLa cells have been irradiated in a beam of π^--mesons using fractionated exposures. The response-time curve for cells irradiated in the peak and in the plateau regions showed evidence of recovery. For cells irradiated in the post-peak position recovery was either absent or delayed.

During the past few years there has been much interest in using π^--meson beams for radiobiological research. The depth-dose curve for a π^--meson beam has an initial plateau region followed by a rise to the peak region after which the dose falls off sharply. We have recently investigated the biological effectiveness at different depths in a π^--meson beam (Mill *et al.*, 1976). In the experiments described in this communication, HeLa cells were exposed to fractionated doses of π^--mesons in order to investigate repair of sub-lethal damage caused by this type of radiation.

MATERIALS AND METHODS

The π^--meson beam used for these experiments is situated at the Rutherford Laboratory, Oxfordshire, and has been described elsewhere (Perry and Hynes, 1971). The dosimetry and cell culture methods used have been previously described (Mill *et al.*, 1976). The depth dose curve for the $\pi-$-beam used for these experiments is shown in Fig. 1. HeLa cells were irradiated in the plateau region, the peak region and in the post-peak region. The dose-rate varied between ~30 and 60 rad/hour, depending on the depth used and on experimental conditions. The irradiation procedure differed from that used for the single dose exposures, and was as follows.

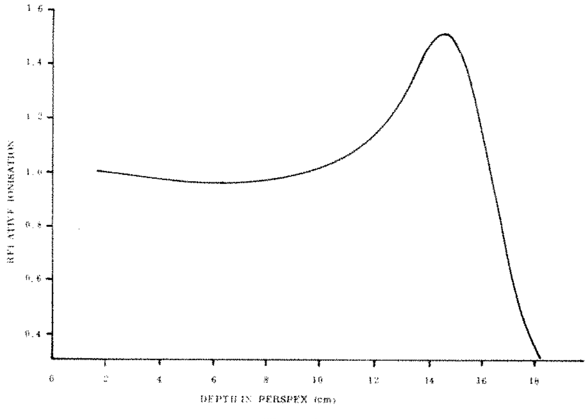

FIG. 1.

Central axis depth dose curve for 70 MeV π^--mesons

Initially 2 cm^3 of cell suspension of concentration $\sim 2\times10^6$ cells/cm^3 were irradiated in each of three positions simultaneously. When the exposure had been given, the beam was switched off and the cell suspensions removed from the beam. Each suspension was then diluted to about 10^5 cells/cm^3 and placed at 37°C. For the second dose, a 2 cm^3 sample was taken from each of the three suspensions, placed in the appropriate position in the beam and irradiated. When the exposure was completed, the samples were removed and replaced by the next ones taken from the diluted suspensions. This process was repeated until a time interval of about 11 hours had elapsed between the first and second doses. The temperature of the cells during irradiation was 21°C. After each sample had received its second dose, the cells were counted, diluted and plated as usual. The experimental details are given in Table I.

RESULTS

Figures 2, 3 and 4 show the results obtained. The data are plotted as a surviving fraction, relative to that of a control sample of cells, as a function of radiation free interval between first and second doses. The plateau region data (Fig. 2) show a fairly large

TABLE I

IRRADIATION DETAILS

Approx. position	Actual depth (cm)	1st dose (rad)	2nd dose (rad)	Approx. dose rate (rad h^{-1})
Plateau	4·8	155	63	29
Plateau	6·7	64	64	38
Front of peak	13·0	211	86	39
Peak	14·9	98	98	59
Back of peak	15·6	205	83	38
Back of peak	16·2	76	76	45

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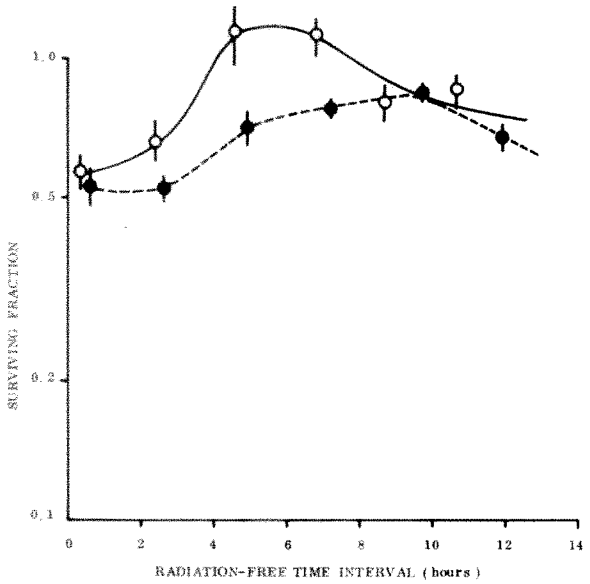

Fig. 2.

HeLa cell recovery curve: plateau position.

○ Dose=64+64 rad; depth=6·7 cm.
● Dose=155+63 rad; depth=4·8 cm.

rise in surviving fraction for times greater than about four hours, followed by a fall in the value of the surviving fraction, *i.e.* the cells appear to be showing the usual oscillatory "Elkind" recovery pattern (Elkind and Sutton, 1959). Data obtained in the peak and front of the peak positions (Fig. 3) indicate similar results. However, the data obtained at depths of 15·6 and 16·2 cm (Fig. 4)—*i.e.*, at the back of the peak—show a different pattern. For the higher doses used (205+83 rad), there is no increase in surviving fraction up to a time interval of 12 hours. At the lower dose, there is an indication of recovery beginning to occur at 9–10 hours, 4–5 hours later than seen in the peak and plateau positions. This effect is not a function of the dose-rate or total dose, as both of these are intermediate between the equivalent values in peak and plateau.

Discussion

The presence or absence of a fractionation effect is dependent on the shape of the single dose survival curve, which in turn is a function of the mean Linear Energy Transfer (LET) of the radiation. Todd (1968) has shown that whenever the single dose survival curve is exponential, two dose response curves do not show recovery. The data presented here show recovery in plateau, peak and pre-peak positions, but no—or at least very much delayed—recovery in the post-peak position. The single dose survival curves are not exponential for any of these positions; nor is irradiation in the post-peak position most effective (see Fig. 5, taken from Mill *et al.*, 1976).

The LET distribution in the peak of a π^--meson extends from about 6 to 1,000 keV/μm (Raju and Richman, 1972) and varies significantly over the peak region. It seems likely that the cells in the post-peak position are in a region where there may be some components of very high-LET radiation

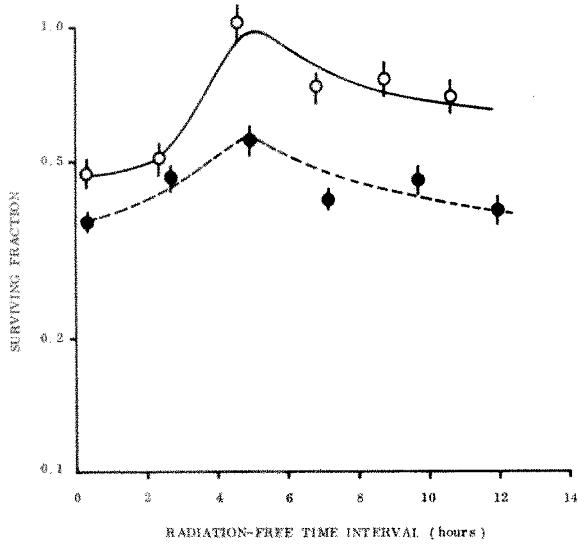

Fig. 3.

HeLa cell recovery curve: peak and front peak position.
○ Dose=98+98 rad; depth=14·9 cm.
● Dose=211+86 rad; depth=13·0 cm.

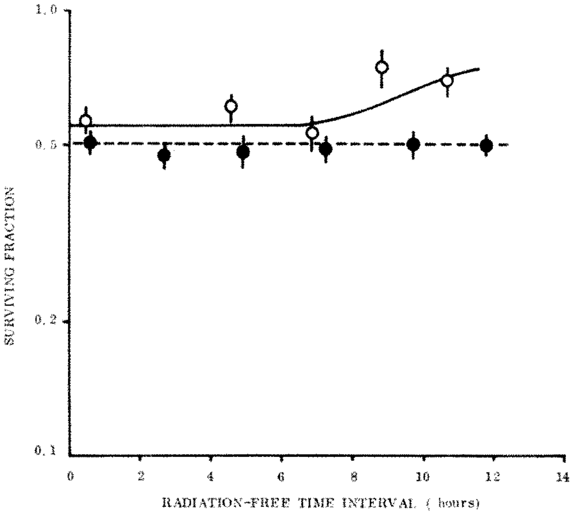

Fig. 4.

HeLa cell recovery curve: back of peak position.
○ Dose=76+76 rad; depth=16·2 cm.
● Dose=205+83 rad; depth=15·6 cm.

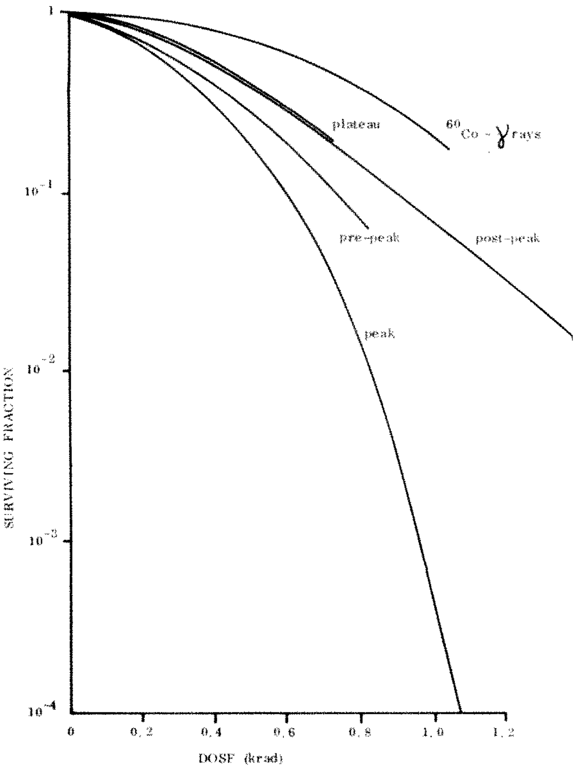

FIG. 5.

Single dose survival curves for irradiation with a beam of π^--mesons (from Mill *et al.*, 1976).

(*i.e.*, > 160 keV/μm). The relative biological effectiveness of the high-LET component would be low (due to saturation) but there would be only a small fractionation effect.

When fast neutrons interact with matter they produce particles that have a wide range of LETs similar to the range of LET given by π^--mesons in the peak. Ellis *et al.* (1970), using 14 MeV neutrons, found that recovery in HeLa cells was delayed some 8–14 hours following the first dose, *i.e.*, a result qualitatively similar to that found for the π^--meson beam in the post-peak position.

It seems we must learn much more of the complex nature with which a π^--meson beam interacts with biological material before any attempt at human radiotherapy is made. The possible effect on normal tissue irradiated outside the peak region must be investigated as thoroughly as the effect on tumour tissue in the peak region before any estimation of the usefulness of π^--meson radiotherapy is made.

ACKNOWLEDGMENTS

The authors wish to acknowledge the help given by the staff of the Rutherford Laboratory, especially Dr. D. H. Reading, Mr. M. A. Hynes and Mr. W. Spinks. The work was supported by a grant from the Cancer Research Campaign.

REFERENCES

ELKIND, M. M., and SUTTON, H., 1959. X-ray damage and recovery in mammalian cells in culture. *Nature*, *184*, 1293.

ELLIS, R. E., LEWIS, J. D., and LINDOP, P. J., 1970. The effect of 14 MeV neutrons on mammalian cells *in vitro*. Abstract 242. *IVth International Congress of Radiation Research*, Evian, France.

MILL, A. J., LEWIS, J. D., and HALL, W. S., 1976. Radiation response of mammalian cells after irradiation with a beam of π^--mesons. *British Journal of Radiology*, *49*, 166–171.

PERRY, D. R., and HYNES, M. A., 1971. A pion beam for radiobiological and dosimetric studies: using a proton synchrotron external target. *CERN Publication 71–16*, *1*, 220.

RAJU, M. R., and RICHMAN, C., 1972. Negative pion radiotherapy: physical and radiobiological aspects. *Current Topics in Radiation Research Quarterly*, *8*, 159.

TODD, P., 1968. Fractionated heavy ion irradiation of cultured human cells. *Radiation Research*, *34*, 378.

1976, *British Journal of Radiology*, *49*, 360–366

A comparison for use in radiotherapy of neutron beams generated with 16 and 42 MeV deuterons on beryllium

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(*Received June, 1975*)

ABSTRACT

The physical and radiobiological properties of two neutron beams have been compared. The beams were generated by deuterons of 16 MeV at Hammersmith Hospital and 42 MeV at Harwell, in both cases falling on a Be/Cu target. The dose-rate and depth-dose characteristics at the higher energy were found to be superior to those at the lower energy. Collimation and shielding at the higher energy are facilitated by the greater degree of forward-peaking and by the fact that a higher dose-rate allows longer collimators to be used. Attenuation in iron was found to be similar at the two energies. The radiobiological properties of the two neutron beams are very similar. There is a difference of about 20 per cent in RBE for effects on mammalian tissues for doses between 300 and 2,000 rad of neutrons. The OER and the sparing effect of two large fractions are the same for the two beams.

A beam of fast neutrons from the MRC cyclotron at Hammersmith Hospital has been in use for radiotherapy since 1966. First impressions of the clinical results have been sufficiently favourable that a randomized prospective trial to compare neutrons with photons was started in 1971. This trial has been confined to certain grades of cancer in the mouth and throat, one of the main reasons for the restriction being the poor penetration of the beam. Although the standard target-skin distance is 120 cm, depth-doses are intermediate between those of 250 kV X rays at 50 cm target-skin distance and ^{60}Co γ rays at 80 cm source-skin distance. Even with these physical limitations a significant improvement in the local response of the tumour after neutron treatment has already become apparent (Catterall *et al.*, 1975). A beam of higher-energy neutrons giving greater penetration would enable a wider spectrum of disease to be treated. With this in mind we have made a preliminary assessment of the relevant physical and radiobiological properties of a neutron beam generated by 42·5 MeV deuterons from the variable energy cyclotron at Harwell, with encouraging results.

PHYSICAL ASPECTS

Dosimetry and dose-rate

Measurements of dose were made with a polythene-walled, ethylene-filled chamber which responds to both neutrons and γ rays, and with photographic film in lead screens which has a sharply reduced sensitivity to fast neutrons and essentially measures the partial dose of γ rays alone (Bewley and Parnell, 1969). Derivation of the partial dose of neutrons is discussed by Greene (1971) and Bewley *et al.* (1972). The polythene/ethylene chamber gives the dose in a material of composition CH_2; this can be converted to dose in tissue by multiplying by the ratio of Kerma (or mass-energy absorption coefficient for neutrons) in tissue to Kerma in CH_2. To do this properly the neutron spectrum is required together with values of Kerma over the range of neutron energy included in the spectrum.

Neutron spectra from thick Be targets bombarded with deuterons of 16, 33 and 50 MeV have been measured by Meulders *et al.* (1975). They found the mean neutron energy to be about 0·4 times the deuteron energy. With both the cyclotrons at Hammersmith and Harwell we used a Be target of thickness 150 mg/cm^2 designed for use with 16 MeV deuterons at Hammersmith. The loss of energy by 42·5 MeV deuterons in this thickness is about 3 MeV and the remaining energy was dissipated in the copper backing. The resulting neutron spectrum is uncertain but the mean energy was probably not far from 18 MeV. Published values of Kerma extend only to 18 MeV (Bach and Caswell, 1968) so that Kerma ratios can be calculated for less than half the spectrum. As the neutron energy rises the cross-section of H falls relative to those of C, N and O and the Kerma in CH_2 falls relative to that in tissue. To convert from ionization in ethylene to dose in soft tissue we have used the Kerma factor calculated for the neutron beam at Hammersmith, of mean energy 7·5 MeV, multiplied by an arbitrary factor of 1·1 to allow for the higher energy (at 18 MeV the factor is 1·05). Use of a tissue-equivalent chamber would not have eliminated all the uncertainty because of the substitution of C for O in tissue-equivalent plastic.

The measured dose-rate at 120 cm was 0·055 rad of neutrons per μ Coulomb on the target, plus an additional contribution from γ rays amounting to 6 per cent of the neutron dose. At 10 μA this gives 33 rad/min. The work of Meulders *et al.* (1975) indicates that a thick Be target would give a dose rate over three times greater. August *et al.* (1973) measured 75 rad/min at 125 cm for 10 μA of 40 MeV deuterons on thick Be. Thus the dose-rate at 10–20 μA would be adequate for treatment even at distances greater than 120 cm.

Collimation and shielding

Field size was selected by means of the wooden collimators used on the neutron beam at Hammersmith which is generated by 16 MeV deuterons on Be. The properties of the collimators at the lower energy have been described by Bewley and Parnell (1969). The rest of the shielding was built with blocks of borated polyester resin of density 1·4 g cm^{-3}, a small section of paraffin wax, and a steel cylinder in front of the target, as shown in Fig. 1.

We made some measurements of attenuation in iron and hydrogenous materials, using a "broad beam geometry", for neutrons generated by 16 MeV deuterons at Hammersmith and 42 MeV deuterons at Harwell. The materials under test were placed at 60–80 cm from the target with a beam collimated to 10–15 cm diameter at this distance. The measurements were made at 125 cm with a pair of ionization chambers to separate the partial doses of neutrons and γ rays. Figure 2 shows the transmitted dose of neutrons and γ rays at the two energies. The upper and lower groups of curves give the neutron and γ ray doses respectively. As expected, the hydrogenous material is markedly less effective in attenuating the neutrons at the higher neutron energy while the effectiveness of iron is barely altered. At both energies, we found that hydrogenous material could be substituted for iron in the outer layers (beyond 5 per cent transmission) with little loss of efficiency. The partial dose of γ rays is always a small fraction of the total and is unlikely to be biologically significant.

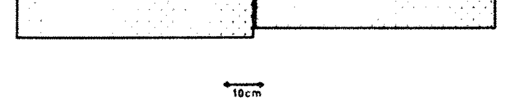

Fig. 1.

Shielding and collimation used with 42 MeV deuterons on a Be/Cu target. Variable Energy Cyclotron at Harwell.

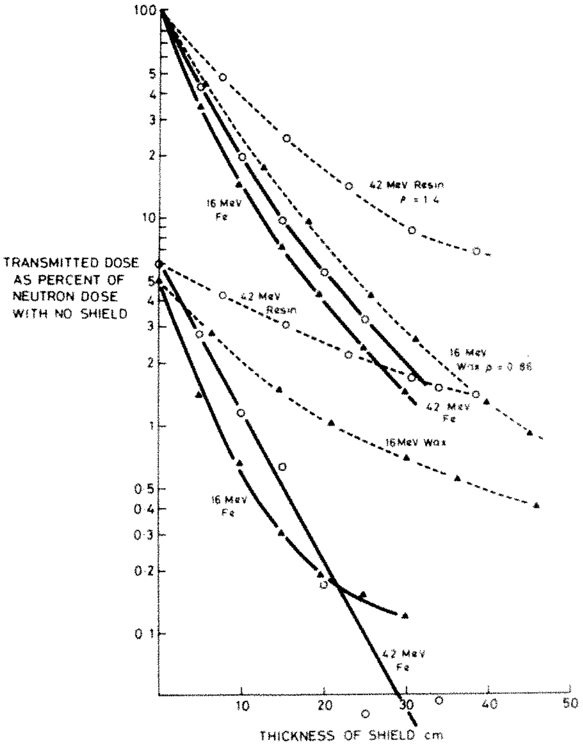

Fig. 2.

Broad beam attenuation curves for shielding of neutrons generated by 16 and 42 MeV deuterons on Be/Cu targets. Dose of neutrons (upper group) and γ rays (lower group) as a percentage of the neutron dose on the beam axis with no shielding. The density of the resin was 1·4 g cm^{-3} and of the wax 0·86 g cm^{-3}.

In spite of the greater penetration of neutrons generated at 42 MeV through hydrogenous materials, wooden collimators 69 cm long surrounded by blocks of resin gave reasonably sharp collimation. The total (neutron plus γ) doses at 10 and 20 cm from the axis using a 7 × 7 cm field were respectively found to be 1·5 per cent and 1 per cent of the dose on the axis. Both Theus *et al.* (1974) and Smith *et al.*

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(1974) also found hydrogenous collimators satisfactory for neutron beams of comparable energies.

Shielding at 42 MeV is made easier by the narrow polar diagram of neutron intensity at high deuteron energy. The fluence of neutrons above 11 MeV was measured by activation of copper, ^{63}Cu (n,2n)^{62}Cu, and was found to fall to 50 per cent at 10 deg., 10 per cent at 28 deg. and 1 per cent at 70 deg. to the forward direction. The 90 per cent level was reached at 3·7 deg. compared with 5·4 deg. for neutrons generated by 16 MeV deuterons on Be.

Skin sparing

The transition curve shown in Fig. 3 was measured at 120 cm from the target with a flat, thin-walled chamber in front of which were placed thin sheets of tissue-equivalent plastic. The curve measured previously with the lower energy neutron beam is also shown. These results at 42 MeV lie between those measured by Almond *et al.* (1973) at 30 and 50 MeV. It is clear that the dose received by the sensitive cells in skin will be smaller when the higher energy neutron beam is used for radiotherapy.

Depth-doses

Depth-doses were measured in tissue-equivalent liquid of density 1·1 (Bewley and Parnell, 1969) with a compensated ionization chamber which responds only to neutrons (Bewley, 1971). The results were converted to unit density tissue as explained by Bewley and Parnell (1969). Gamma rays were measured with film in lead screens as mentioned above. Central-axis values for three field sizes are shown in Fig. 4 together with a neutron curve measured at the lower neutron energy for comparison. The depth-dose curve for the partial dose of γ rays is also shown for the 21×21 cm field. The better penetration of the higher energy beam is clear; at 10 cm deep to a 12×12 cm field, for example, the percentage depth dose is 63 per cent compared to 46 per cent at the lower energy. The partial dose of γ rays amounts to about 10 per cent of the local neutron dose for the 21×21 cm field but gives a smaller contribution with smaller fields. These γ-ray doses are maximum values for two reasons:

(1) the neutron sensitivity of the film has been ignored, and

(2) the emulsion shows some response to thermal neutrons in the phantom, which recent work suggests may entail a correction of about 15 per cent.

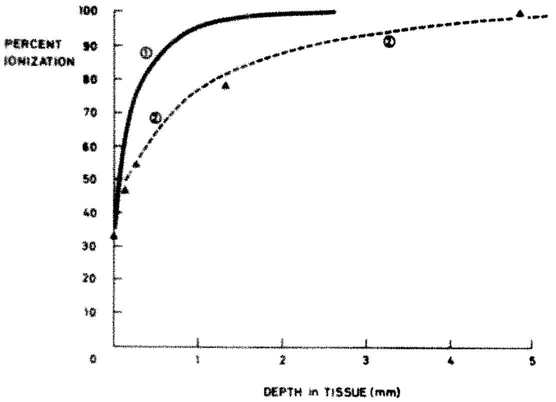

FIG. 3.

Transition curves of neutrons generated by 16 MeV (①) and 42 MeV (②) deuterons on Be/Cu targets.

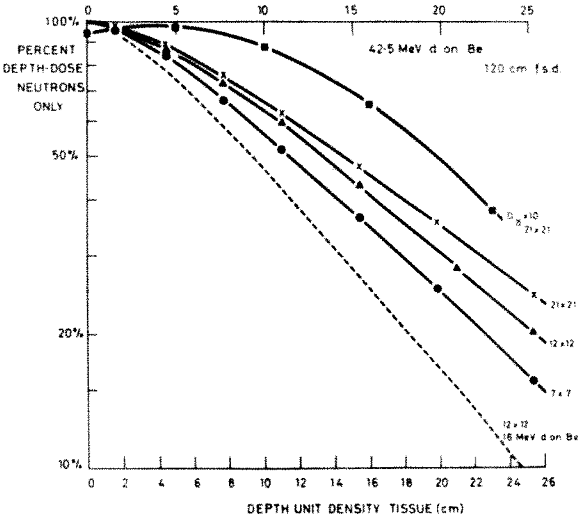

FIG. 4.

Neutron and γ-ray depth doses in unit density tissue, as a percentage of the neutron dose at the surface. The γ-ray curve is drawn on scale ×10. A neutron curve for the lower energy beam (16 MeV deuterons on Be) is also given for comparison.

The neutron depth-doses are very close to those measured at 140 cm by Smith *et al.* (1974) with 50 MeV deuterons on a thick Be target. A direct comparison is impossible however because of the thin target used by us and because Smith *et al.* did not distinguish between the partial doses of fast neutrons and γ rays.

A complete isodose chart was also measured for the 12×12 cm field. This had rounded lines showing that a flattening filter would be needed, as expected from the forward emission of the beam (see above).

RADIOBIOLOGICAL ASPECTS

The purpose of our short series of radiobiological measurements was to compare the neutron beams generated by 16 and 42 MeV deuterons with respect

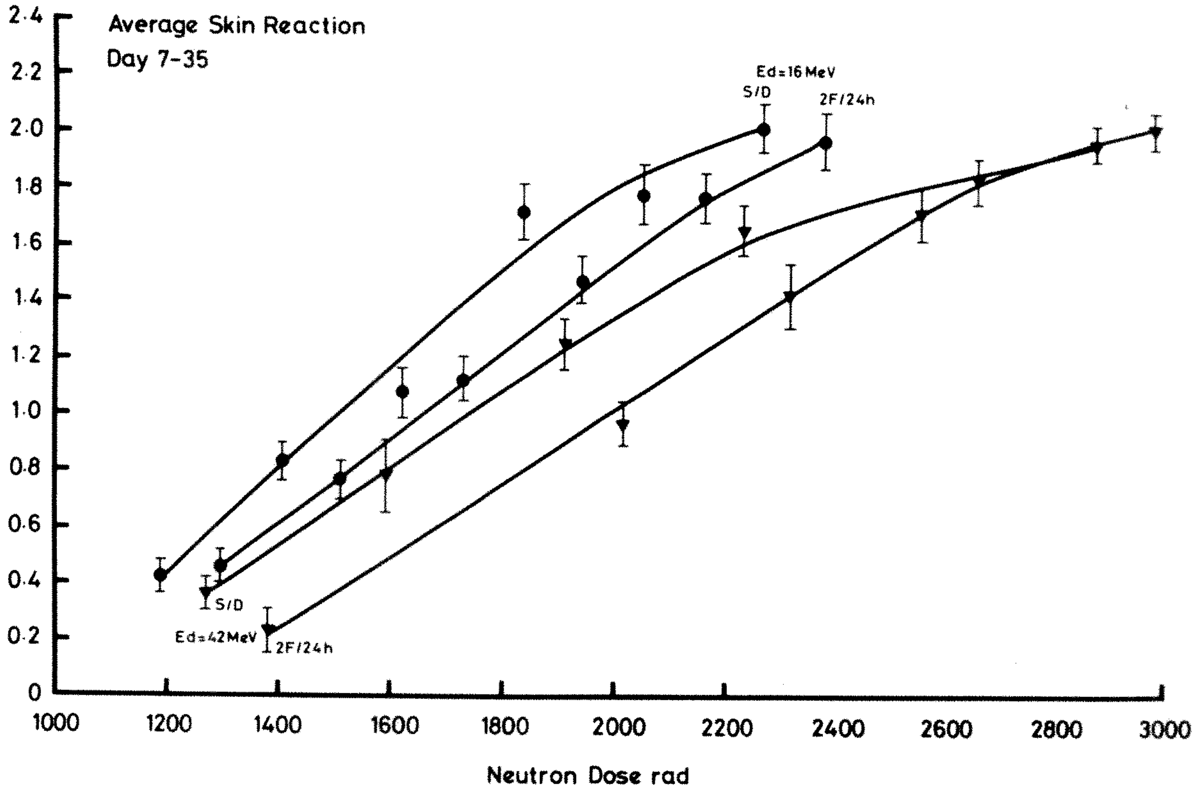

FIG. 5.

Dose effect curves for early skin reactions in the feet of mice irradiated with a single dose or two equal fractions at 24 hours. The abscissa is the dose of neutrons alone.

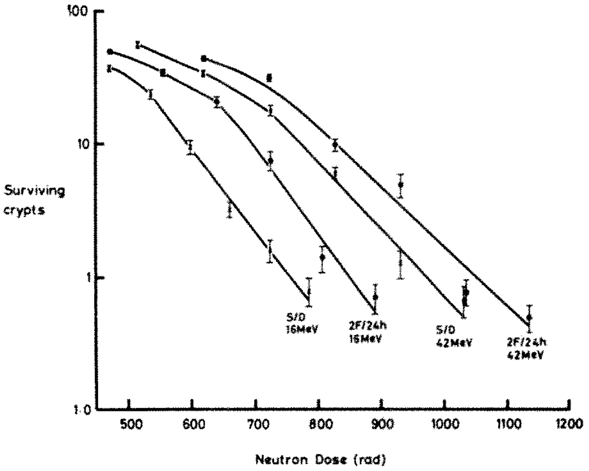

FIG. 6.

Survival of jejunal crypts in mice after irradiation with a single dose or two equal fractions at 24 hours. The abscissa is the dose of neutrons alone.

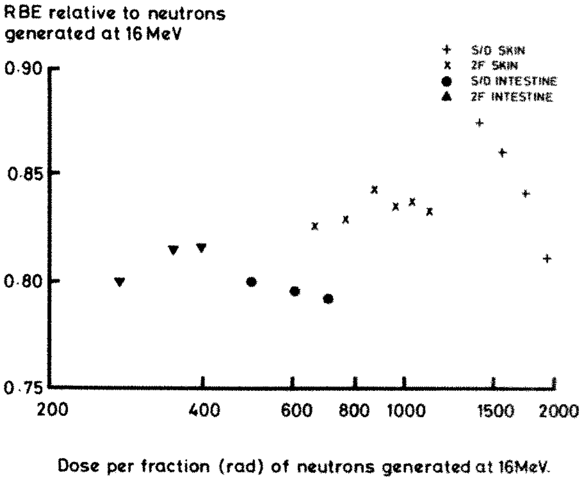

FIG. 7.

RBE of neutrons generated by 42 MeV deuterons compared with neutrons generated by 16 MeV deuterons given in one or two fractions, for early skin reactions in feet and survival of crypts in the ileum and jejunum of mice.

to relative biological effectiveness (RBE), the sparing effect of fractionation, and oxygen enhancement ratio (OER). Skin reactions and survival of intestinal crypts in mice were used as indicators of RBE and fractionation, while cells in suspension were used to measure OER.

Skin reactions and survival of intestinal crypts

For irradiation of skin, female mice of strain "CFLP", obtained from Anglia Laboratory Animals Ltd., were arranged round the edge of a collimator and lightly held in position by taping the toes with Sellotape. One hind foot of each mouse was irradiated while the rest of the body was shielded. Tissue-equivalent plastic was placed next to the feet to give secondary charged-particle equilibrium. The mice were divided into two groups and irradiations with the two beams were given on the same day, with the same technique of irradiation. The early wave of skin reactions was assessed in numerical terms over a period of 7–35 days. The techniques of irradiation and assessment have been described by Field *et al.* (1967). The dose-effect curves for a single dose (S/D) and two equal fractions at 24-hour separation (2F/24h) are shown in Fig. 5. In both cases the "dose" is the partial dose of neutrons alone. Corrections were applied for the non-uniformity of the higher energy neutron beam (0·955) and for the reduced sensitivity of the ionization chamber (0·9) as discussed above.

For the measurement of survival of intestinal crypts, female CFLP mice were divided into two groups and were given whole-body irradiation on successive days by one or other of the two neutron beams. The animals were killed at five days after

Table I

Ehrlich ascites cells all *in vitro*

Radiation	8·7 deep in phantom			No phantom		
	D_0 Aerobic	D_0 Anoxic	OER (mean and 95% confidence limits)	D_0 Aerobic	D_0 Anoxic	OER (mean and 95% confidence limits)
Neutrons from 16 MeV deuterons on Be/Cu	85	162	1·9 (1·7–2·1)	90	160	1·8 (1·6–2·0)
Neutrons from 16 MeV deuterons on Be/Cu	55	110	2·0 (1·8–2·2)	64	117	1·8 (1·6–2·1)
250 kV X rays	—	—	—	184	516	2·8 (2·6–3·0)
250 kV X rays	—	—	—	207	546	2·6 (2·4–2·8)
250 kV X rays	126	337	2·7 (2·6–2·8)	132	357	2·7 (2·6–2·8)
Neutrons from 42 MeV deuterons on Be/Cu	99	193	2·0 (1·8–2·1)	114	198	1·7 (1·6–1·9)
Gain factor 16 MeV			1·38			1·50
42 MeV			1·35			1·59

TABLE II

Lymphocytic leukaemia cells irradiated *in vitro* and assayed *in vivo*

Radiation	8·7 deep in phantom			No phantom		
	D_0 Aerobic	D_0 Anoxic	OER (mean and 95% confidence limits)	D_0 Aerobic	D_0 Anoxic	OER (mean and 95% confidence limits)
Neutrons from 16 MeV deuterons on Be/Cu	84	132	1·6 (1·4–1·8)	84	158	1·9 (1·7–2·1)
8 MV X rays	142	353	2·5	151	346	2·3
Neutrons from 42 MeV deuterons on Be/Cu	116	173	1·5	93	164	1·8
RBE $\frac{42\text{ MeV}}{16\text{ MeV}}$	0·73	0·76	—	0·90	0·96	—
Anoxic gain factor 16 MeV			1·86			1·37
42 MeV			1·73			1·44

irradiation and the surviving crypts in the ileum and jejunum were counted. Details of the assay technique are given by Hornsey (1973). The number of surviving jejunal crypts is shown as a function of neutron dose in Fig. 6, after applying corrections similar to those used for irradiation of skin. Similar results were obtained for the ileum.

RBE values for both end points are combined in Fig. 7. The mean value for the RBE of the higher energy neutron beam compared with the lower is about 0·83 ±0·1. There was no significant difference between the values obtained from surviving crypts in the ileum or jejunum or from skin reactions, nor was there any significant difference between the RBE measured with one or two fractions. These results are supported by those of Withers *et al.* (1974) who found the RBE of neutrons generated at 50 MeV relative to those generated at 16 MeV to be 1/1·33 or 0·75, again independent of the number of fractions or the level of dose.

Cells in suspension

We have used two cell lines from mice: Ehrlich ascites and P388 lymphocytic leukaemia cells. In both cases the cells were irradiated in suspension in Perspex tubes through which a slow stream of gas was passed to stir the cells and maintain a constant degree of oxygenation. The technique is that devised by McNally and Bewley (1969). The cells were exposed under aerobic and hypoxic conditions, with no phantom present and at 8·7 cm deep in tissue-equivalent liquid, using a 12 × 12 or 12 × 14 cm field. The Ehrlich ascites cells were cultured and assayed *in vitro* as described by Cullen (1972). The lymphocytic leukaemia cells were assayed *in vivo* by serial dilution as described by Berry (1968). Similar experiments have been performed at different times with neutrons generated by 16 MeV deuterons on Be at Hammersmith, and also with X rays. In all cases the total time of irradiation was about the same, the dose-rate being adjusted to make the longest exposure of hypoxic cells about 1½ hours.

The results of all these experiments are given in Tables I and II. D_0 is the dose for survival to e^{-1} on an exponential survival curve. The values of D_0 represent the local neutron doses at the cells. The additional partial doses of γ rays are given in Table III. The two neutron energies give similar values of OER for both cell lines. When the cells were exposed out of the phantom the anoxic gain factor (the ratio OER for photons to OER for neutrons) was about 1·5 for the ascites cells and 1·4 for the lymphocytic leukaemia cells. In the phantom the gain factor of 1·4 measured with the ascites cells was rather less than the value measured out of the phantom, whereas the leukaemia cells gave a much greater gain factor in than out of the phantom, 1·8 compared to 1·4, in agreement with previous measurements with this system (Berry, 1971). Variations in OER for neutrons in or out of a phantom will be discussed in greater detail elsewhere (Berry and Bewley, 1976). The important point in the context of the present paper is that the change in neutron energy between the two beams did not significantly change the OER for either cell line under a given condition of irradiation. This is supported by the results of Hall *et al.* (1974) using Chinese hamster cells *in vitro* who found the same OER for neutrons generated by 35 and 50 MeV deuterons as for neutrons generated by 16 MeV deuterons.

TABLE III

Maximum value of γ-ray dose as a fraction of neutron dose

	Hammersmith	Harwell
No phantom	0·04	0·06
In phantom	0·12	0·10

Discussions and Conclusions

The work described in this paper was intended to be a preliminary assessment of the potential value for radiotherapy of a neutron beam generated with 42 MeV deuterons. It was designed to answer the question "what are the physical and radiobiological differences between neutron beams generated with 42 and 16 MeV deuterons?" We planned a strictly limited series of experiments to elucidate the main relevant factors.

In spite of the higher neutron energy, we found that it is still possible to provide good shielding and collimation. This is made easier by the pronounced forward-peaking of the beam while the high intensity allows longer collimators to be used if necessary. The degree of skin-sparing is better than that obtainable with the neutron beam generated at 16 MeV. The depth doses at 120 cm are markedly superior to those at the lower energy and are intermediate between those of ^{60}Co γ rays and X rays generated at 4 MV, both at 100 cm.

The radiobiological properties of the two neutron beams are very similar. There is a difference of about 20 per cent in RBE for effects on mammalian tissues for doses between 300 and 2,000 rad of neutrons. The OER and the sparing effect of two large fractions are the same for the two beams.

It seems from these experiments that a neutron beam generated by 42 MeV deuterons for radiotherapy would be substantially superior to one generated at 16 MeV.

ACKNOWLEDGMENTS

We are glad to acknowledge the great help given to us by the operating team of the VEC, and particularly to Mr. E. J. Jones for much help with organizational problems and for measuring the polar diagram of neutron production. We would also like to thank Mrs. C. Morris, Mr. P. Warren, Mrs. L. Manjil and others for technical assistance. The biological assays using the P-388 leukaemia cells were carried out at the Churchill Hospital Research Institute, Oxford, whilst one of the authors (R. J. Berry) was a member of the MRC External Scientific Staff.

REFERENCES

ALMOND, P. R., SMATHERS, J. B., OLIVER, G. D., HRANITZKY, E. B., and ROUTT, K., 1973. Dosimetric properties of neutron beams produced by 16–60 MeV deuterons on beryllium. *Radiation Research, 54*, 24–34.

AUGUST, L. S., THEUS, R. B., ATTIX, F. H., BONDELID, R. O., SHAPIRO, P., SURRATT, R. E., and ROGERS, C. C., 1973. Fast neutron dose rate as a function of incident deuteron energy for $D+{}^9Be$. *Physics in Medicine and Biology, 18*, 641–647.

BACH, R. L., and CASWELL, R. S., 1968. Energy transfer to matter by neutrons. *Radiation Research, 35*, 1–25.

BERRY, R. J., 1968. Hypoxic protection and recovery in tumour cells irradiated at low dose rates and assessed *in vivo*. *British Journal of Radiology, 41*, 921–926.

1971. Hypoxic protection against fast neutrons of different energies—A review. *European Journal of Cancer*, 7, 145–152.

BERRY, R. J., and BEWLEY, D. K., 1976. Change in oxygen enhancement ratios with depth in tissue-equivalent material for a collimated beam of fast neutrons. *British Journal of Radiology* (in press).

BEWLEY, D. K., 1971. Physical characteristics of fast neutron beams. *European Journal of Cancer*, 7, 99–104.

BEWLEY, D. K., and PARNELL, C. J., 1969. The fast neutron beam from the MRC Cyclotron. *British Journal of Radiology, 42*, 281–288.

BEWLEY, D. K., MCCULLOUGH, E. C., PAGE, B. C., and SAKATA, S., 1972. Determination of absorbed dose in a fast neutron beam by ionisation and calorimetric methods. *Proceedings of the First Symposium on Neutron Dosimetry in Biology and Medicine*, 159–175.

CATTERALL, M., BEWLEY, D. K., and SUTHERLAND, I., 1975. First results of a randomised clinical trial of fast neutrons and X or gamma rays (photons) in the treatment of advanced tumours of the head and neck. *British Medical Journal*, 653–656.

CULLEN, B., 1972. A transient change in the radiosensitivity of mammalian cells resulting from a change in the pre-irradiation culture conditions. *International Journal of Radiation Biology, 21*, 583–594.

FIELD, S. B., JONES, T., and THOMLINSON, R. H., 1967. The relative effects of fast neutrons and X rays on tumour and normal tissue in the rat. *British Journal of Radiology, 40*, 834–842.

GREENE, D., 1971. An ionisation chamber for the dosimetry of 14 MeV neutron beams. *Physics in Medicine and Biology, 16*, 489–496.

HALL, E. J., NOVAK, M. S., and MARINO, S. A., 1974. Comparative radiobiological measurements with two high-energy cyclotron-produced neutron beams presently used for radiotherapy. *British Journal of Radiology, 47*, 882–887.

HORNSEY, S., 1973. The effectiveness of fast neutrons compared with low LET radiation on cell survival measured in the mouse jejunum. *Radiation Research, 55*, 58–68.

MCNALLY, N. J., and BEWLEY, D. K., 1969. A biological dosimeter using mammalian cells in tissue culture and its use in obtaining neutron depth dose curves. *British Journal of Radiology, 42*, 289–294.

MEULDERS, J. P., LELEUX, P., MACQ, P. C., and PIRART, C., 1975. Fast neutron yields and spectra from targets of varying atomic number bombarded with deuterons from 16 to 50 MeV. *Physics in Medicine and Biology, 20*, 235–243.

SMITH, A. R., ALMOND, P. R., SMATHERS, J. B., and OTTE, V. A., 1974. Dosimetric properties of the fast neutron therapy beams at TAMVEC. *Radiology, 113*, 187–193.

THEUS, R. B., BONDELID, R. O., ATTIX, F. H., AUGUST, L. S., SHAPIRO, P., SURRATT, R. E., and ROGERS, C. C., 1974. Physical characteristics of the NRL fast neutron beam for radiation therapy. *Cancer, 34*, 17–32.

WITHERS, H. R., MASON, K., REID, B. O., DUBRAVSKY, N., BARKLEY, H. T., BROWN, B. W., and SMATHERS, J. B., 1974. Response of mouse intestine to neutrons and gamma rays in relation to dose fractionation and division cycle. *Cancer, 34*, 39–47.

1976, *British Journal of Radiology*, 49, 367–371

The use of *Drosophila* to estimate the possibility of genetic hazard from ultrasound irradiations

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(*Received July, 1975 and in revised form September, 1975*)

Abstract

Flies of the species *Drosophila melanogaster* have been irradiated with 1 MHz ultrasound at intensities of 0·05–2 W cm^{-2}. The flies were immersed in water and rotated in the ultrasound field to ensure that they were adequately exposed to the radiation. Immersion and rotation alone were not found to impair subsequent survival and fertility of the flies. At the higher intensities of irradiation, the flies were found to be killed in direct proportion to the duration of the irradiation. However, large-scale breeding experiments with flies surviving irradiation showed that no significant increase in the frequency of recessive lethal mutation (Muller 5 system) and chromosomal non-disjunction (Clark-Sobels system) had occurred. Taken with other recent studies, this result suggests there is little risk of genetic damage to multicellular organisms from ultrasound irradiations at frequencies and intensities currently used in medical practice.

The establishment of techniques utilizing ultrasonic radiation for clinical diagnosis has stimulated several recent attempts to estimate the possibility of genetic hazard from exposure to the radiation. Little precise information is available upon the interaction of ultrasound and tissue, and many conflicting reports of biological "effects" exist (for a review of genetic effect, see Thacker, 1973).

The assessment of genetic effects after ultrasonic irradiation of the fruit fly, *Drosophila*, provides an example of this situation. In the late 1940s a group of American workers demonstrated induction of both lethal and visible mutations after irradiation of adult flies (*e.g.*, Bushnell and Wallace, 1948), and similar results have more recently been reported by Kato (1966), but Fritz-Niggli and Böni (1950) found no increase in lethal mutation frequency after irradiation of eggs, larvae and pupae with 0·3–1·8 W cm^{-2} at 800 kHz for up to 25 minutes. A possible criticism of the positive reports is that they appear to have been obtained through the use of high radiation intensities; these would lead to considerable internal heating of the flies, and heat shock can be mutagenic (see Thacker, 1973).

As part of an extensive programme to assess genetic effects of ultrasound (Baker and Thacker, 1973), a re-examination of the responses of *Drosophila* was undertaken. This multicellular organism is especially useful in that not only gene mutation, but also non-disjunction leading to loss or gain of chromosomes (aneuploidy) can be assessed (for a recent appraisal, see Sobels, 1974). Aneuploidy is associated with as much as one-quarter of human spontaneous abortions (Carr, 1970) and about 0·3 per cent of live births (Smith and Jacobs, 1970), constituting a considerable genetic load upon the population. However, as previously found for single-cell systems utilized in this laboratory (Buckton and Baker, 1972; Thacker, 1974), no increase in the frequency of genetic events was produced by ultrasonic irradiation of *Drosophila*.

Materials and Methods

Biological

Strains of the fruit-fly, *Drosophila melanogaster*, were maintained on oats-sucrose-nutrient agar medium with added yeast at 25°C in milk-bottles.

1. *Detection of recessive lethal mutations.* The Muller-5 (M5) system was employed, with methods closely following those of the original study (Spencer and Stern, 1948). Briefly, the wild-type male flies (strain Oregon K) were treated and mass-mated to M5 virgin females, and their progeny (F$_1$), after a short period of "ageing" in mass, were mated incestuously (one female to one or more males in small vials). Their progeny (F$_2$) were assessed for the presence or absence of wild-type male flies; complete absence of the latter flies with at least 10 male M5 progeny present was the criterion for recognition of a recessive lethal mutational event having occurred. All presumed lethals were checked in F$_3$ matings, where the same criterion pertained. Stocks of flies were kindly supplied by Dr. M. J. Fahmy.

2. *Detection of non-disjunction.* The system of Clark and Sobels (1973) was used, where flies carrying isochromosomes may "rescue" oocytes suffering from non-disjunction of Chromosome 2. Virgin females with isochromosome markers *j;px* were treated within four hours of eclosion and mated to males of the isochromosome strain *b pr;vg*. Ten

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males were mated to 10 females per vial with an ample supply of yeast for two days, and then transferred (without etherization) to milk bottles for a further three days before discarding. All F_1 progeny were screened for the exceptional (parental) types which result from the rescued oocytes. We are grateful to Professor F. H. Sobels for suggesting the use of this system and to Dr. B. Leigh for supplying the isochromosome strains.

Ultrasound generation and measurement

A radio-frequency generator was used to drive a ceramic transducer of resonant frequency 1 MHz (Brush Clevite PZT 5A). This transducer was positioned to radiate horizontally through a waterbath, with a rubber mat at the opposite end of the bath for absorption. The total power of the ultrasound beam was found from measurements of the radiation force on a suspended steel ball, and the distribution of intensity found using a hydrophone probe (Hill, 1970).

Experimental procedure

Flies were etherized and placed in a modified polystyrene syringe, as shown in Fig. 1a. After allowing the flies to recover fully from the ether, water (at 25°C) was rapidly drawn into the syringe, completely immersing the flies. The syringe was then positioned in the water tank at the centre of the ultrasound field and 10 cm from the transducer. As far as possible, small air bubbles were eliminated from the compartment containing the flies, and latterly a wetting agent was included in the water. During irradiation, the syringe was rotated at 15 rev./minute to compensate for differences in the spatial distribution of intensity within the syringe. A scan of the ultrasound field inside the syringe is shown in Fig. 1b.

Immediately after treatment, the water was expelled from the syringe and the flies removed onto filter paper (to promote rapid drying). The flies were then put into mating bottles or vials, and placed at 25°C.

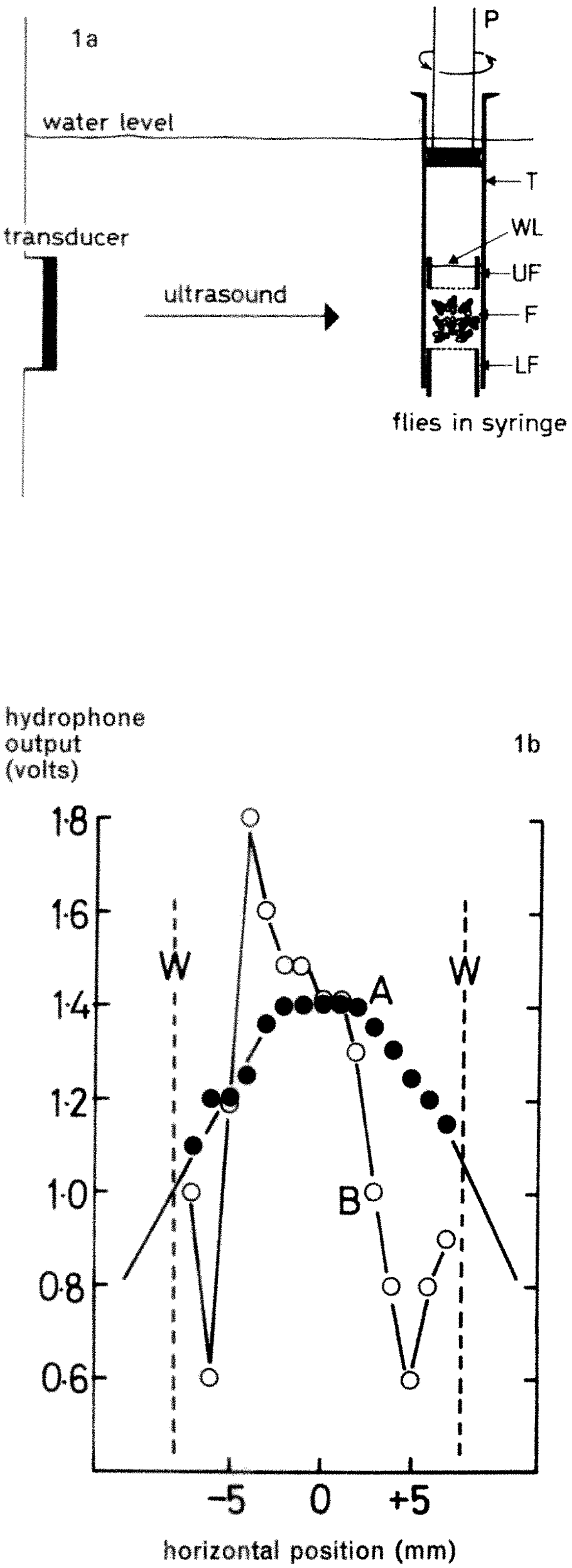

Fig. 1.

Irradiation methods and measurements.

(a) Diagram of irradiation apparatus showing a modified syringe containing the flies positioned in the ultrasound field P = plunger, T = syringe tube, WL = water level in the syringe, UF = upper sliding filter, F = flies, LF = lower sliding filter.

(b) Hydrophone scan of intensity distribution across ultrasound field (peak intensity 1 W cm^{-2} at 1 MHz). A = without syringe in position, B = inside syringe. W = wall of syringe tube.

Results

Lethality

Drosophila is a very convenient organism for genetic studies, but it is not aquatic and the flies were expected to suffer from the immersion required to propagate the radiation. However, although the flies had every appearance of being dead after immersion without irradiation (having a very bedraggled appearance and no limb movements), they revived in a time approximately equal to the duration of immersion. Fertility was also unimpaired subsequent to immersion.

When irradiated with the higher intensities used in the present study, the immersed flies were killed in an approximately linear proportion to the duration of irradiation. A survival curve is shown for the male wild-type flies of the Muller-5 system (Fig. 2); the females irradiated to assess non-disjunction were found to be about twice as sensitive as this (see next section).

A crude measurement of the heat rise inside an irradiated fly was made by threading a dead fly with a fine thermocouple, and placing it in the ultrasound field. The maximum heat rise inside the fly for the intensities used was determined to be around 1·5°C.

Mutation

In both systems the frequency of mutation was first assessed in untreated populations of flies. In addition to this "spontaneous" frequency, mutation was assessed in flies subjected to immersion and rotation alone (that is, under identical conditions to the irradiated flies but without irradiation). Irradiations were mostly at "therapeutic" levels (0·5–2·0 W cm^{-2} for a few minutes), but the Muller-5 system was also tested at a low intensity for a longer continuous irradiation time (to simulate certain diagnostic procedures).

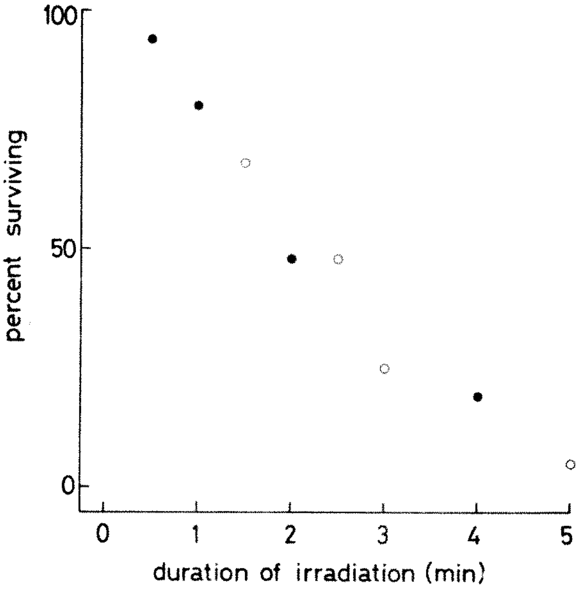

Fig. 2.

Survival of male wild-type flies after 1 MHz irradiation at 2 W cm^{-2}. Different symbols indicate separate experiments.

1. *Recessive lethal mutation.* The spontaneous frequency at which recessive lethals are detectable varies slightly from strain to strain (Spencer and Stern, 1948) and with the stringency of the criteria used to accept the occurrence of a mutagenic event. An average value from many previous studies has been given as 0·26 per cent (Crow and Temin, 1964), and it is seen that the present study yielded a very similar frequency (Table I). No significant increase upon this frequency was found in irradiated flies; from the combined data given in Table I it may be calculated that a minimum of 19 lethal mutants must be found after ultrasound treatment for a significant difference to be recognized at the 1 per cent probability level (see Kastenbaum and Bowman, 1970).

Since certain spermatogenic stages have been shown to be more sensitive to mutagenic agents such as X-rays (*e.g.* Muller *et al.*, 1954), a small-scale test was made of flies remated five to seven days after irradiation at 0·5 W cm^{-2}. The mature sperm released at this time would have been in meiotic or earlier stages of spermatogenesis when irradiated. However, no lethal mutations were found among 755 crosses examined.

2. *Non-disjunction.* Clark and Sobels (1973) have reported a spontaneous frequency of 9·4 oocytes suffering non-disjunction of Chromosome 2 per thousand assessed in the first five days after mating. Although this frequency is subject to some variation with the hatchability of the fertilized eggs, the frequency obtained in the present study was very similar (Table II). Very few of the female flies used in this system survived intensities exceeding 0·5 W cm^{-2}, so that only one dose-point was satisfactorily tested. This showed no increase in non-disjunction frequency over controls (Table II); for a significant increase to be recognized, at the 1 per cent level, at least 55 non-disjunction progeny should have been found after ultrasound treatment.

Fewer progeny resulting from oocytes lacking Chromosome 2 (nullosomic) than from those having two copies of this chromosome (disomic) were found after immersion and rotation of the flies, irrespective of the irradiation. This ratio was also found to vary in the study of Clark and Sobels (1973), possibly due

TABLE I

FREQUENCY OF SEX-LINKED RECESSIVE LETHAL MUTATIONS DETERMINED BY MULLER-5 SYSTEM

Experimental treatment	Number of experiments	Total crosses assessed	Total lethals detected	Lethals per thousand crosses
None (untreated control)	1	1,174	3	2·56
1 MHz for 5–10 min.				
0·5 W cm^{-2}	4	2,342	5	2·14
1·0 W cm^{-2}	2	1,596	4	2·51
2·0 W cm^{-2}	1	1,015	1	0·99
Control (immersed and rotated)	3	3,644	6	1·65
1 MHz for 60 min.				
50 mW cm^{-2}	2	1,613	3	1·86
Control (immersed and rotated)	1	954	1	1·05
Combined results				
Controls	5	5,772	10	1·73
Irradiated	9	6,566	13	1·98

TABLE II

FREQUENCY OF NON-DISJUNCTION OF CHROMOSOME 2 DETERMINED BY THE METHOD OF CLARK AND SOBELS (1973)

Experimental treatment	Number of crosses attempted	Total progeny	Non-disjunction progeny		Non-disjunctions per thousand progeny
			disomic	nullosomic	
None (untreated control)	21	4,093	17	21	9·28
1 MHz for 2–10 min. (mostly 5 min.)					
0·5 W cm^{-2}	31	5,064	28	16	8·69
1·0 W cm^{-2}	17	605	1	1	(3·31)
Control (immersed and rotated)	19	4,133	25	11	8·71

to reduced viability of the progeny resulting from "rescue" of nullosomic oocytes (*b pr;vg*) under some circumstances.

DISCUSSION

In a previous report (Thacker, 1974) it was stressed that few genetic data were available upon the effects of irradiating multicellular organisms with ultrasound. The recent report upon the induction of gross mutational damage in mice (Lyon and Simpson, 1974), taken with the present report, suggests no detectable genetic damage arises in such organisms irradiated with medically-relevant "doses" of ultrasound.

The present data agree with, and considerably extend, those of Fritz-Niggli and Böni (1950) who irradiated non-adult stages of *Drosophila* and scored relatively few crosses for the presence of sex-linked lethal mutations. In addition, both male and female flies were irradiated in the present study; that is, the sensitivity of both spermatozoa and oocytes was assessed. Although a "positive control" was not included (*i.e.*, a treatment with a known mutagenic agent), both systems show well-defined responses to such agents as ionizing radiation (see Spencer and Stern, 1948; Clark and Sobels, 1973).

It seems unlikely that the negative results of ultrasound irradiation arise from inadequate exposure of the flies to the radiation. The rotation procedure should eliminate or, at least, reduce inhomogeneity of irradiation, and the killing of flies in proportion to dose suggests this is successful. The small heating effect of irradiations in the present study suggests internal heating is unlikely to account for the death of the flies, and mechanical effects of the radiation may be responsible (*cf.* Wells, 1968).

In all, there seems to be little evidence that ultrasound irradiations produce genetic damage; the studies noted in this report cover a variety of genetic changes from small alterations in genes ("point mutations"), through deletion and rearrangement of genes, to effects on whole chromosomes. Although extrapolation to man remains a difficulty, organisms such as *Drosophila* and the mouse are at present the most useful experimental models for the assessment of genetic effects of unknown agents upon man. The lack of an effect of ultrasound upon these organisms, therefore, represents a current best estimate of lack of hazard to man.

ACKNOWLEDGMENTS

We are indebted to the Medical Research Council for support, and we are most grateful to Beryl Derbyshire for her skilful assistance in maintaining and handling the flies for these experiments.

REFERENCES

BAKER, N. V., and THACKER, J., 1973. Tests for direct or indirect mutagenic effects of ultrasound. *Mutation Research*, *21*, 22–23.

BUCKTON, K. E., and BAKER, N. V., 1972. An investigation into possible chromosome damaging effects of ultrasound on human blood cells. *British Journal of Radiology*, *45*, 340–342.

BUSHNELL, R. J., and WALLACE, R. H., 1948. Induction of sex-linked mutations in *Drosophila* with ultrasonic treatment. *Anatomical Record*, *101*, 690.

CARR, D. H., 1970. Chromosome abnormalities and spontaneous abortions. In *Human Population Genetics*, edited by P. A. Jacobs, W. H. Price and P. Law, pp. 103–118 (Edinburgh University Press).

CLARK, A. M., and SOBELS, F. H., 1973. Studies on non-disjunction of the major autosomes in *Drosophila melanogaster*. I. Methodology and rate of induction by X-rays for the compound second chromosome. *Mutation Research*, *18*, 47–61.

CROW, J. F., and TEMIN, R. G., 1964. Evidence for partial dominance of recessive lethal genes in natural populations of *Drosophila. American Naturalist*, *98*, 21–33.

FRITZ-NIGGLI, H., and BÖNI, A., 1950. Biological experiments on *Drosophila melanogaster* with supersonic vibrations. *Science*, *112*, 120–122.

HILL, C. R., 1970. Calibration of ultrasonic beams for bio-medical applications. *Physics in Medicine and Biology*, *15*, 241–248.

KASTENBAUM, M. A., and BOWMAN, K. O., 1970. Tables for determining the statistical significance of mutation frequencies. *Mutation Research*, *9*, 527–549.

KATO, M., 1966. Inductivity of recessive lethal mutations in *Drosophila melanogaster* by ultrasonic vibration. *Osaka Medical School Bulletin*, *12*, 108–113.

LYON, M. F., and SIMPSON, G. M., 1974. An investigation into the possible genetic hazards of ultrasound. *British Journal of Radiology*, *47*, 712–722.

MULLER, H. J., HERSKOWITZ, I. H., ABRAHAMSON, S., and OSTER, I. I., 1954. A non-linear relation between X-ray dose and recovered lethal mutations in *Drosophila. Genetics*, *39*, 741–749.

SMITH, P. G., and JACOBS, P. A., 1970. Incidence studies of constitutional chromosome abnormalities in the postnatal population. In *Human Population Cytogenetics*, edited by P. A. Jacobs, W. H. Price and P. Law, pp. 159–189 (Edinburgh University Press).

SOBELS, F. H., 1974. The advantages of *Drosophila* for mutation studies. *Mutation Research*, *26*, 277–284.

SPENCER, W. P., and STERN, C., 1948. Experiments to test the validity of the linear R-dose/mutation frequency relation in *Drosophila* at low dosage. *Genetics*, *33*, 43–74.

THACKER, J., 1973. The possibility of genetic hazard from ultrasonic radiation. *Current Topics in Radiation Research Quarterly*, *8*, 235–258.

1974. An assessment of ultrasonic radiation hazard using yeast genetic systems. *British Journal of Radiology*, *47*, 130–138.

WELLS, P. N. T., 1968. The effect of ultrasonic irradiation on the survival of *Daphnia magna*. *Experimental Biology*, *49*, 61–70.

1976, *British Journal of Radiology*, *49*, 372–373

Technical note

The assessment of the body distribution of Yttrium-90 ferric hydroxide during radiation synovectomy

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(*Received October, 1975*)

In recent years, the use of radionuclides for intra-articular therapy has become widespread. Of ^{198}Au and ^{90}Y, the two most commonly used isotopes, the latter is preferred in knee treatments due to the longer range of the β particles and the absence of γ radiation. In this department, we have attempted to measure the loss of the isotope from the knee, and to determine the location of any missing activity following treatment with the colloid ^{90}Y ferric hydroxide. Such information is necessary in assessing the therapeutic efficiency and the radiation hazard of the treatment.

In order to minimize the loss of the isotope from the knee, the patients were confined to bed for five days and wore a Plastazote splint following the injection. 5 mCi of ^{90}Y ferric hydroxide in 10 ml. was the standard dose.

The activity in the knee was measured in terms of the geometric mean of the count-rates in two opposed (medial and lateral) 2×2 in. scintillation crystals. The system was set to detect bremsstrahlung, produced by the slowing down of the ^{90}Y β particles, with an energy of more than 60 keV. Tests indicated that the most significant source of error in these measurements was due to the effect of bone on bremsstrahlung production and attenuation as the colloid distributed itself within the knee.

The search for the ^{90}Y which escaped from the knee was made with a Mecaserto scanner fitted with a 5×3 in. crystal. To obtain the highest sensitivity when investigating the abdominal region, the focusing collimator was removed from the scanning head. This modification increased the count rate from a ^{90}Y bremsstrahlung source at the focus by a factor of about 10, while the spatial resolution deteriorated to 15 cm (F.W.H.M.). Reduction of the skin-detector distance, which was possible without the focusing collimator, increased the sensitivity further and improved the spatial resolution to about 10 cm. For a qualitative investigation of the sort undertaken the poor spatial resolution was not a problem. Under the chosen conditions of scan speed (1·3 cm/second) and integration time (0·4 second), the instrument was capable of detecting less than 1 per cent of the knee activity in the regional lymph-nodes even in the presence of knee background. No attempt was made to quantify the ^{90}Y in locations other than the knee.

Knee loss figures from eight patients treated with ^{90}Y ferric hydroxide have been obtained. After one and five days, the average loss values were 6 and 21 per cent respectively. These results compare well with those of Gumpel *et al.* (1975), who obtained values of 6 and 22 per cent. By comparison with previous work at this hospital (Ramsey, 1973), it appears that the retention of the ^{90}Y ferric hydroxide is less than that of the resin or silicate preparations.

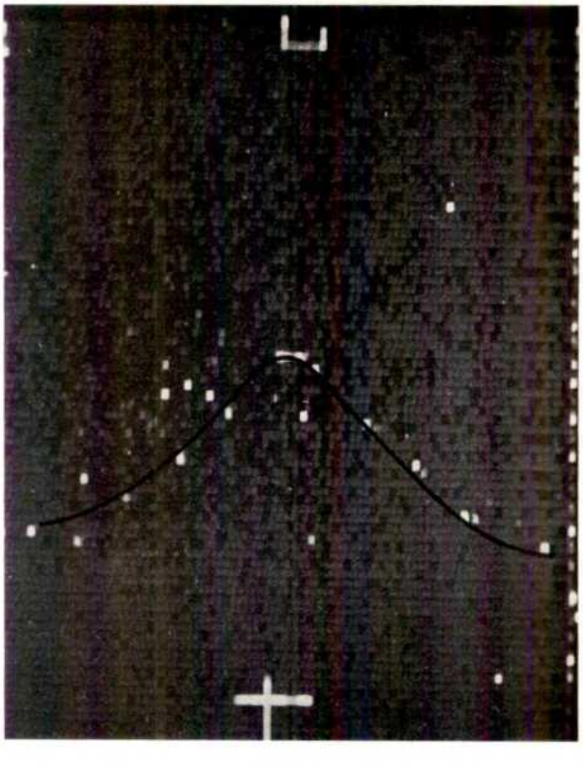

Fig. 1.

Scan showing uptake of ^{90}Y ferric hydroxide in the liver. The positions of the supra-sternal notch, the costal margin and the umbilicus are shown. Increased count-rate is indicated by the darker shade. Isolated white spots are spurious.

In four of the patients, the knee counts increased in the first five hours, illustrating the effect of the redistribution of the isotope in the knee.

Four of the eight patients were subjected to the scanning procedure described above. All four showed leakage to the regional lymph-nodes within six days. In two of the four cases, the scan indicated leakage after five hours when the knee counts had actually increased. Leakage to the liver was clearly demonstrated in one patient after five days, Fig. 1. Another patient showed activity covering the whole abdominal area.

REFERENCES

Gumpel, J. M., Beer, T. C., Crawley, J. C. W., and Farran, H. E. A., 1975. Yttrium-90 in persistent synovitis of a knee—a single centre comparison. The retention and extra-articular spread of four ^{90}Y colloids. *British Journal of Radiology*, *48*, 377–381.

Ramsey, N. W., 1973. Retention of ^{90}Y in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *32, Supplement to No. 6*, 38–40.

1976. *British Journal of Radiology*, *49*, 374–376

Case reports

Pulmonary arterial aneurysms in association with a right ventricular myxoma

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(*Received August, 1975*)

Aneurysms of the pulmonary artery are uncommon and have been described as mycotic, congenital, syphilitic, traumatic and idiopathic (Boyd and McGavack, 1939). Aneurysms have not previously been described in association with a right-sided cardiac myxoma. This is a report of such a case and it is suggested that when pulmonary arterial aneurysms are diagnosed by pulmonary angiography, a right atrial injection should also be made to exclude an intracardiac source of emboli.

CASE HISTORY

The patient, an 18-year-old Cretan student, was admitted to the Brompton Hospital in September 1973 with an 18-month history of a relapsing febrile illness which had previously been investigated in Crete and also in Athens. He had been well until January 1972, when he presented with rigors and a swinging pyrexia. No formal diagnosis was made at that time and he was treated with antibiotics. The fever remitted but subsequently returned at monthly intervals lasting about seven days. In October 1972 he had one bright red haemoptysis and a chest radiograph taken at the time showed a 10 cm round shadow at the left base. In December 1972, in Athens, a left lower lobectomy was performed with excision of this lesion. Histology was reported as: "a haemorrhagic cyst with no evidence of malignancy". He was discharged from hospital but his recurrent febrile episodes persisted accompanied by arthralgia and pleuritic pain. He was given numerous further courses of antibiotics. In April 1973 a chest radiograph showed that a small round shadow was now present at the right base. Percutaneous aspiration biopsy was attempted and only blood could be aspirated from the lesion. The patient refused further diagnostic procedures at that time. He came to England in September 1973 with no change in his symptoms.

There was no other past medical history, nor history of industrial exposure. He had taken no medication prior to this illness and in particular had received no intravenous injections either from a medical practitioner or himself.

EXAMINATION

He was a normally built white male. He was febrile, 99–102°F, but his general condition was otherwise good. There were signs of the left thoracotomy but the chest was otherwise clear. The pulse was regular with a rate of 110 per minute. Blood pressure was 100/80Hg. At the time of admission, a short high pitched diastolic murmur was heard at the left sternal edge but this finding could not subsequently be confirmed. The remainder of the physical examination was entirely normal.

INVESTIGATIONS

Haematological examination revealed a Hb of 10·4 G per cent with a normochromic normocytic film. Reticulocytes were 2 per cent. The white cell count was 6,500 with a normal differential. The platelets were normal. The E.S.R. was 67 mm/h (Westergren).

The examination of the bone marrow showed an increased cellularity, active granulopoesis and very active normoblastic erythropoesis. Haemoglobin electrophoresis was normal. Glucose-6-phosphate dehydrogenase activity was normal. No malarial parasites were seen on repeated thick films.

Normal biochemical estimations included: urea, electrolytes, calcium, phosphate, liver function tests, and protein electrophoresis. Urinary V.M.A. and 5 H.I.A.A. were normal. The immunoglobulins were IgG 1325 (500–1500) IgA 450 (125–450) IgM 430 (50–170). Blood and urine cultures failed to grow any pathogenic organisms on many occasions. Urine microscopy was normal. Mantoux test was negative at a strength of 1:1,000 but positive at 1:100.

Serology for the following organisms was negative: salmonella, influenza, adenovirus, respiratory syncytial virus, *Coxiella burnetti*, psittacosis, mycoplasma, hydatid disease,

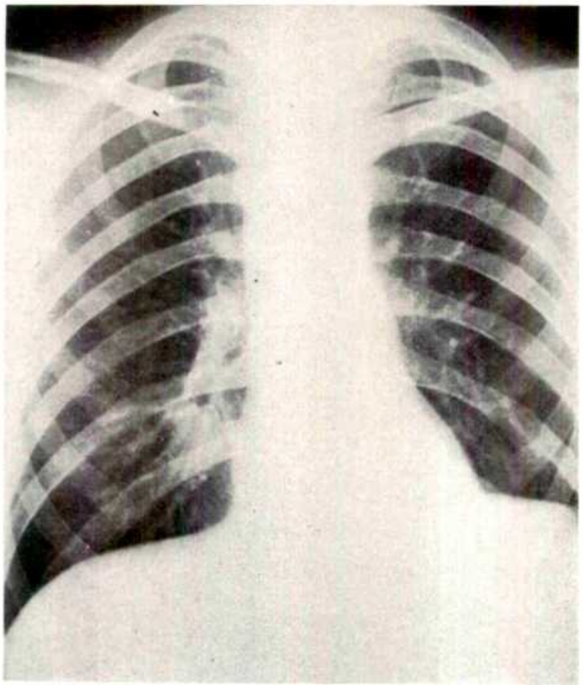

FIG. 1.

Chest radiograph showing 2½ cm round opacity in the right lower zone. A left lower lobectomy has been performed.

brucella, toxoplasma, filaria, schistosoma, amoebiasis, aspergillus, histoplasma and candida.

Anti-nuclear and other auto-antibodies and L.E. cells were not found in the blood. W.R., V.D.R.L., R.P.C.F.T. and Rheumatoid factor tests were negative. The E.C.G. in sinus rhythm was normal. An echocardiogram revealed a small left atrium, and a normal mitral valve. There was no evidence of a left atrial myxoma, but the right side of the heart was not examined.

Chest X-ray (Fig. 1) showed a 2½ cm round opacity in the right lower zone, with quite obvious loss of peripheral vasculature at the right base. Frontal and lateral tomography of the right lower zone (Fig. 2) showed a round opacity with a smooth well-defined outline and a pulmonary arterial branch leading to it. No definite draining vein could be identified.

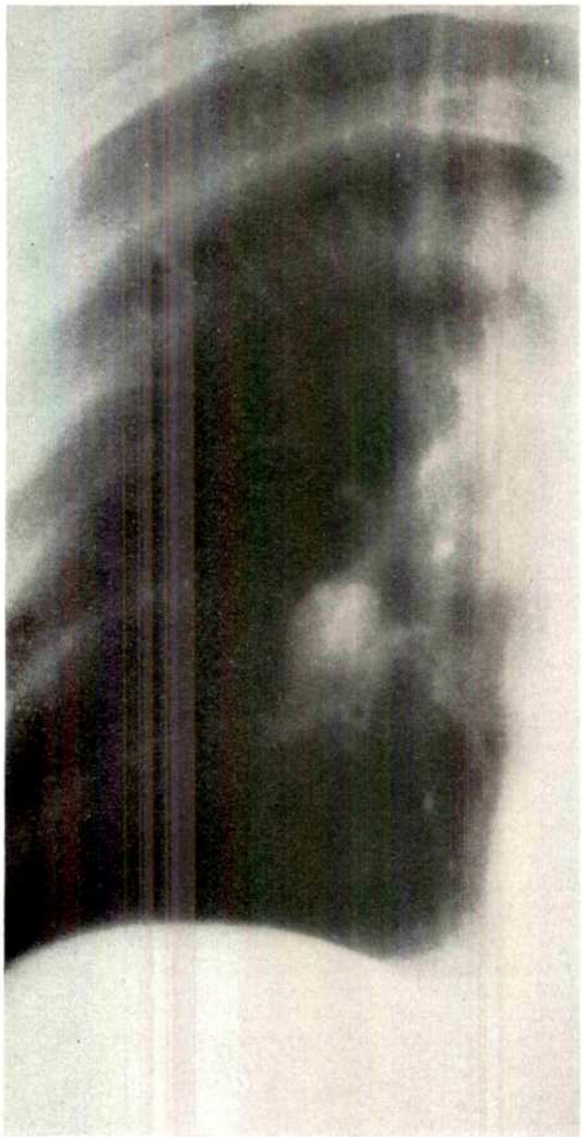

FIG. 2A.

Antero-posterior tomogram shows the lesion in the right lower lobe, and loss of peripheral vasculature.

PROGRESS

The patient remained febrile with fevers reaching 102·5° on most days. On four occasions crops of tender, red indurated nodules appeared in the skin of his forearms and fingers. These were biopsied and on microscopy slight lymphocytic and plasma cell cuffing of the small blood vessels was seen, but there were no specific diagnostic features. No bacteria could be cultured from these lesions. On two occasions he had sudden attacks of hypotension associated with central cyanosis. There was spontaneous recovery within five minutes on both occasions.

Cardiac catheterization and pulmonary angiography were performed. Pressures in the right atrium, main pulmonary artery and wedged pulmonary artery were normal. The pulmonary angiogram (Fig. 3) showed complete occlusion of one of the main branches of the basal artery of the right lower lobe. The vessel terminated in an aneurysmal dilation 2 cm by 1½ cm corresponding to the opacity seen in the plain radiograph. Two smaller aneurysms were seen lateral to the large one. There was no early filling of veins to suggest an arteriovenous shunt. The left atrium, left ventricle and aorta appeared normal.

In view of the finding of aneurysms of the pulmonary artery, the possibility that these might be secondary to a lesion in the right side of the heart was considered. An injection of contrast medium (Fig. 4) was therefore made into the right atrium and a large filling defect in the right ventricle apparently arising from the interventricular septum was seen. A mobile projection of this defect was seen moving in and out of the pulmonary outflow tract in time with the cardiac cycle.

A diagnosis of right ventricular tumour was therefore made and a thoracotomy performed. A white jelly-like

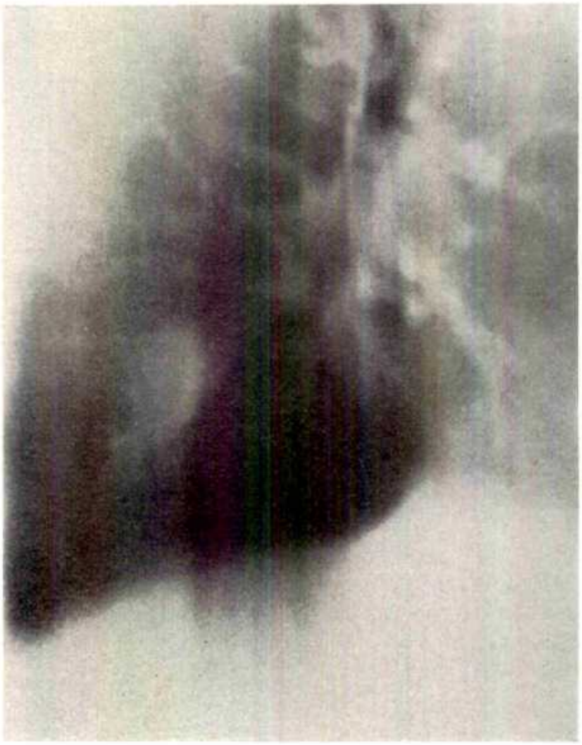

FIG. 2B.

Lateral tomogram.

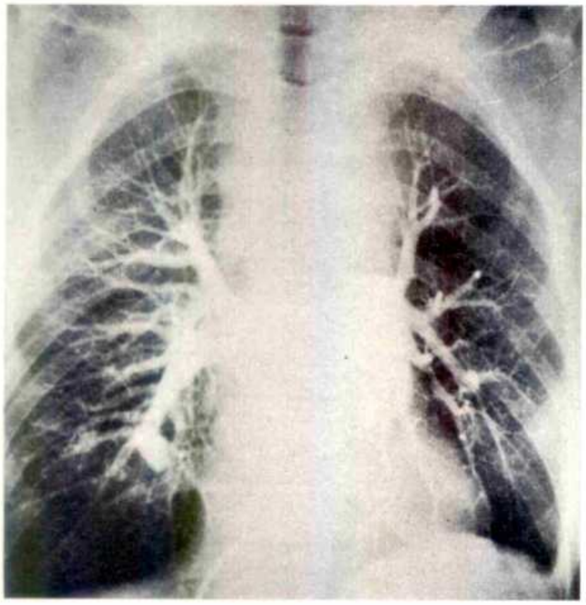

Fig. 3.

Pulmonary arteriogram. Three aneurysms are demonstrated in the right lower lobe. Lack of filling of vessels peripheral to the lesions is also seen.

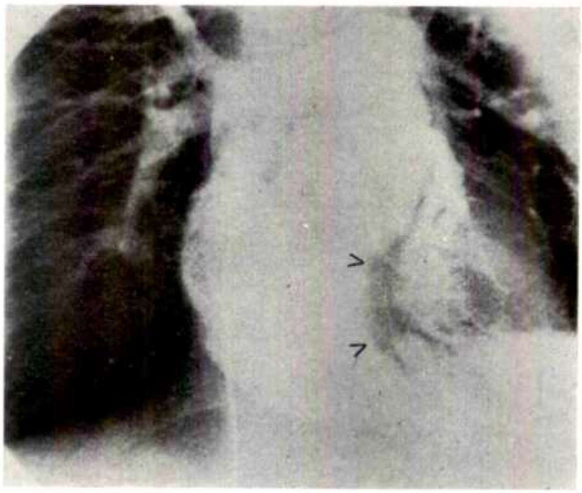

Fig. 4.

Cine frame of right atrial injection of contrast showing large filling defect in the right ventricle.

tumour was found broadly based on the papillary muscle of the conus and the adjacent right ventricle. This was excised and portion of myocardium and conus resected down to apparently normal muscle. A patent foramen ovale was found and this was closed. Histology of the tumour showed it to have the characteristic appearance of a cardiac myxoma. There was no evidence of micro-organisms nor fungi in the material and nothing was grown on culture.

The patient made a satisfactory post-operative recovery.

Discussion

In this case the presumption is that myxomatous emboli from the right ventricle invaded the pulmonary arterial wall with resulting aneurysm formation. Obviously histology of the aneurysmal wall would be needed to confirm this, but there is support for this presumption from observations in patients with a left ventricular myxoma. New *et al.* (1970) described systemic arterial aneurysms in association with a left-sided cardiac myxoma. Histology of these aneurysms showed infiltration of the arterial wall with myxomatous tissue. In the pulmonary circulation this has not been reported. However, Heath and Mackinnon (1964) reported a case of multiple fatal pulmonary emboli secondary to a right atrial myxoma in which myxoma tissue could be seen actively infiltrating the media of the pulmonary arteries at autopsy. There was thinning and rupture of the internal and external elastic lamina, although no aneurysm formation was seen. It is therefore considered likely that in the case described above, myxoma emboli similarly weakened the pulmonary arterial wall and this resulted in aneurysm formation.

As a result of experience gained from this case it is recommended that the finding of pulmonary arterial aneurysms should lead to investigation of the right side of the heart by angiography.

Acknowledgment

We would like to thank Professor M. Turner-Warwick for permission to report this case.

REFERENCES

Boyd, L. J., and McGavack, T. H., 1939. Aneurysms of the pulmonary artery: a review of the literature and report of two new cases. *American Heart Journal, 18,* 562–578.

New, P. F. J., Price, D. L., and Carter, B., 1970. Cerebral angiography in cardiac myxoma. *Radiology, 96,* 335–345.

Heath, D., and Mackinnon, J., 1964. Pulmonary hypertension due to myxoma of the right atrium. *American Heart Journal, 68,* 227–235.

1976, *British Journal of Radiology*, *49*, 377–379

Excretion of radioactivity in breast milk following ^{99}Tc^{m} –Sn Polyphosphate

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(*Received August, 1975*)

There are several reports of excretion of radioactivity in the breast milk of mothers given ^{99}Tc^{m}-labelled radiopharmaceuticals (Vagenakis *et al.*, 1971; Berke *et al.*, 1973; Wyburn, 1973; Carmody and Highman, 1975). This report describes excretion of radioactivity in breast milk following intravenous administration of ^{99}Tc^{m} stannous polyphosphate. This has not been previously reported. Lactating women should not be given radioactive substances unless exceptional circumstances exist. We would like to report the following case.

Case history

A 31-year-old married coloured American woman was admitted for investigation of right hip pain present for eight months; the pain had started during her recent pregnancy. Labour was complicated by severe backache and right hip pain. She delivered, spontaneously, a normal live female child weighing 3·7 kg. Breast feeding was established satisfactorily.

The right hip pain got worse, spread across the base of the spine, with severe limitation of movement and weight-bearing. She developed night sweats. At three years of age she had had pulmonary tuberculosis. She was admitted, together with the six-month old baby, for further investigation.

On examination she was afebrile. The breasts were active. She had a peculiar gait. All movements of the right hip were painful; the right femoral head was tender. There was 90 deg. hip flexion. No abnormal glands were palpable.

Relevant investigations

Haemoglobin 11·1 g/100 ml.; WBC normal; ESR 40 mm/hour; uric acid 4·5 mg/100 ml.; Mantoux test—positive to 1:1,000 dilution Old Tuberculin. Radiographs of chest and pelvis, and tomograms of right hip and upper femur showed no abnormality.

A bone scan was requested because it was thought that the patient could have tuberculosis of the right hip which was not obvious radiologically. This was discussed with the clinicians concerned as the patient, although weaning the baby, was still giving it three to four breast feeds daily. The patient was given 10 mCi ^{99}Tc^{m} stannous polyphosphate (Diagnostic Isotopes Incorporated) and a 5:1 minified whole-body scan was performed three hours later using an Ohio-Nuclear Model 84 whole-body scanner fitted with 5 × 2 in. NaI(Tl) detectors. The bladder was emptied immediately before the scan. The postero-anterior bone scan (Fig. 1) showed increased uptake of radioactivity in the right sacro-iliac region and a diagnosis of osteitis condensens

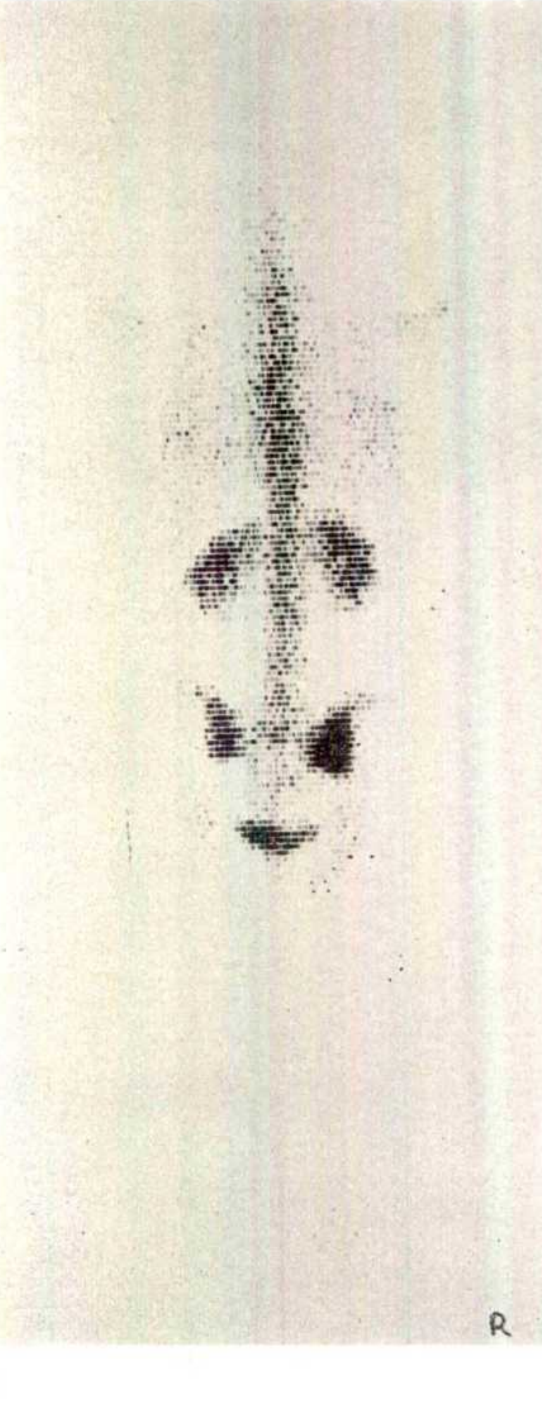

FIG. 1.

Postero-anterior whole-body bone scan three hours after 10 mCi ^{99}Tc^{m} polyphosphate. Note increased uptake in right sacro-iliac joint.

ilii was considered. Manipulation of both sacro-iliac joints was carried out under general anaesthetic with symptomatic improvement.

The antero-posterior scan (Fig. 2) showed unusual concentration of radioactivity in the region of the breasts. The patient expressed 100 ml. of milk from both breasts five hours after the administration of the $^{99}Tc^{m}$ polyphosphate, and the milk was found to contain about 0·2 per cent of the injected activity. In order to avoid radiation hazard to the baby, the patient did not feed or cuddle her baby until the following morning, and she had not done so from the time of injection.

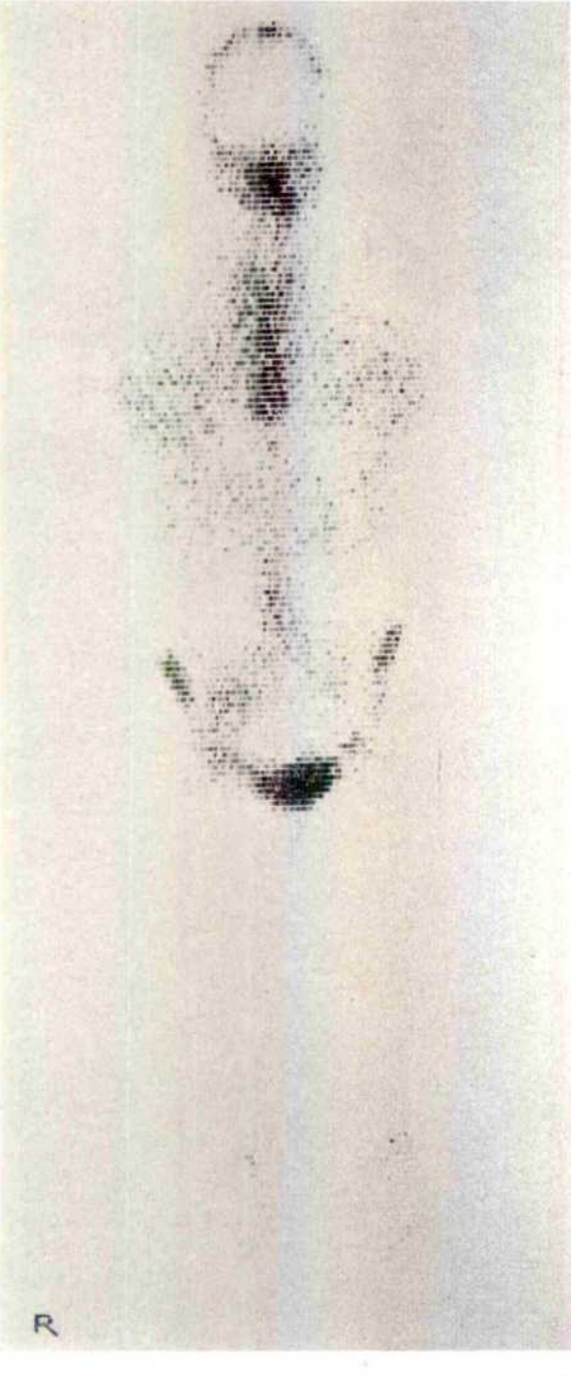

Fig. 2.

Antero-posterior whole-body bone scan three hours after 10 mCi $^{99}Tc^{m}$ polyphosphate. Note unusual uptake in the breast region.

Discussion

When radionuclides are administered to nursing mothers, it is important to assess and minimize the radiation hazard to the baby. James *et al.* (1974) have estimated absorbed doses to children receiving intravenously-administered radiopharmaceuticals, although estimates for oral administration are not available. If the six-month-old baby had been fed at the time of expression, the range of absorbed doses which could have been received (since estimates are available only for the neonate and one-year-old) are 2·09–7·15 mrad to the bone (critical organ) and 0·616–1·65 mrad to the whole body, assuming that the absorbed doses are the same for oral and intravenous administration.

It was not possible to analyse the sample of breast milk to ascertain whether the activity was due to radio-labelled polyphosphate or to free pertechnetate, which the manufacturers (Diagnostic Isotopes Incorporated) claim to be less than 2 per cent. If the radioactivity in the milk was due to free pertechnetate, using the data of James *et al.* (1974) the absorbed doses are estimated to be: 14·3–37·4 mrad to the critical organ (thyroid) and 0·561–1·54 mrad to the whole body. Injected pertechnetate is known to circulate in the blood pool and concentrates in the salivary glands, thyroid, liver and stomach (ICRP Publication No. 17, 1971). In the absence of significant concentration of radioactivity in these sites on the whole-body scans, breast activity was likely to be due to uptake of polyphosphate rather than free pertechnetate.

The exact mechanism of uptake of phosphate complexes in tissue is not known. Schmitt *et al.* (1974) have shown by histochemical staining the presence of increased acid and alkaline phosphatases in biopsied breast tissue of women showing breast uptake of $^{99}Tc^{m}$ stannous diphosphonate and polyphosphate. It has been suggested that these enzymes act as tissue receptors that bind $^{99}Tc^{m}$ stannous disphosphonate and its analogues (Zimmer *et al.*, 1974) and this may be relevant in the case reported here.

ACKNOWLEDGMENTS

We are grateful to Mrs. Diana Spencer, superintendent radiographer, and the members of the Radioisotope Scanning Unit who carried out the scans. We wish to thank Mr. Kirwan, orthopaedic surgeon, for permission to publish details of this case, and also Dr. E. W. Emery, Director of Radiotherapy Department, for encouragement and advice.

REFERENCES

BERKE, R. A., HOOPS, E. C., KEREIAKES, J. C., and SAENGER, E. L., 1973. Radiation dose to breast feeding child after mother has ^{99m}Tc–MAA lung scan. *Journal of Nuclear Medicine*, *14*, 51–52.

CARMODY, R., and HIGHMAN, J. H., 1975. Uptake of pertechnetate in mammary tissue and thyroid after pregnancy. *British Journal of Radiology*, *48*, 63–64.

INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION. Publication No. 17, 1971. *Protection of the patient in radionuclide investigations*. (Pergamon Press, Oxford).

JAMES, A. E., WAGNER, H. N., and COOKE, R. E., 1974. *Paediatric Nuclear Medicine* (W. B. Saunders Company, London).

SCHMITT, G. H., HOLMES, R. A., ISITMAN, A. T., HENSLEY, G. T., and LEWIS, J. D., 1974. A proposed mechanism for ^{99}Tc^{m} labelled polyphosphate and diphosphonate uptake by human breast tissue. *Radiology*, *112*, 733–735.

WYBURN, J. R., 1973. Human breast milk excretion of radionuclides following administration of radiopharmaceuticals. *Journal of Nuclear Medicine*, *14*, 115–117.

VAGENAKIS, A. G., ABREAU, Cynthia M., and BRAVEMOR, L. E., 1971. Duration of radioactivity in the milk of a nursing mother following ^{99}Tc^{m} administration. *Journal of Nuclear Medicine*, *12*, 188.

ZIMMER, A. M., ISITMAN, A. T., and HOLMES, R. A., 1974. Enzymatic inhibition of diphosphonate: a proposed mechanism of tissue uptake. *Journal of Nuclear Medicine*, *16*, 352–356.

Hyperprolactinaemia as a cause of gallium-67 uptake in the breast

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(*Received September, 1975*)

Mammary tissue uptake of Gallium-67 (^{67}Ga) is well recognized (Larson *et al.*, 1973; Gelrud and Arseneau, 1973). A patient is presented in whom such accumulation led to the discovery of drug-induced hyperprolactinaemia.

Case history

A 19-year-old girl with Hodgkin's "Paragranuloma" involving neck glands was successfully treated with radiotherapy in 1969. Five years later a recurrence in neck and inguinal glands, together with diffuse lung mottling, responded to combination therapy with mustine, vincristine, procarbazine and prednisolone.

In mid-1974 she was admitted to hospital in acute renal failure following three weeks of malaise, anorexia, nausea and vomiting. Renal biopsy demonstrated interstitial nephritis of unknown aetiology. Treatment with prednisolone resulted in complete clinical and biochemical resolution within four months.

During admission a total body scan using 2 mCi ^{67}Ga citrate was performed at 48 and 72 hours to identify any sites of recurrent Hodgkin's disease. Uptake was noted in both kidneys and both breasts (Fig. 1). Accumulation of ^{67}Ga in the first sites was attributed to the inflammation of interstitial nephritis.

The mammary activity was unexpected. The patient was not pregnant, but had missed two periods before the return of normal menstrual cycles. She had not taken oral contraceptives. There was no inflammation of the breasts, nor galactorrhoea. Her serum prolactin, however, was grossly elevated: >63 ng/ml. (range: 0–15 ng/ml.). This was explained by the almost continuous doses of anti-emetic drugs which she had been given since admission, *viz*: Stemetil (prochlorperazine) daily, Maxolon (metoclopramide) initially, and Largactil (chlorpromazine) occasionally. On the day ^{67}Ga was injected for the scan she had received intramuscular Stemetil (50 mg) and Largactil (50 mg).

A repeat ^{67}Ga scan four months later showed no breast or other abnormal accumulation (Fig. 2). Basal and thyrotrophin releasing hormone (TRH) stimulated prolactin levels were then normal (9 ng/ml. at 0 minute; >63 ng/ml. at 20 minutes; 37 ng/ml. at 60 minutes) while the thyrotrophin (TSH) response to TRH was low normal (1·7 μU/ml. at 0 minute; 5·7 μU/ml. at 20 minutes; 4·1 μU/ml. at 60 minutes; basal range 0–3 μU/mg.). Circulating thyroid hormone levels were always normal.

DISCUSSION

This case demonstrates the potent influence of high prolactin levels on promoting ^{67}Ga accumulation by mammary tissues. Such accumulation has

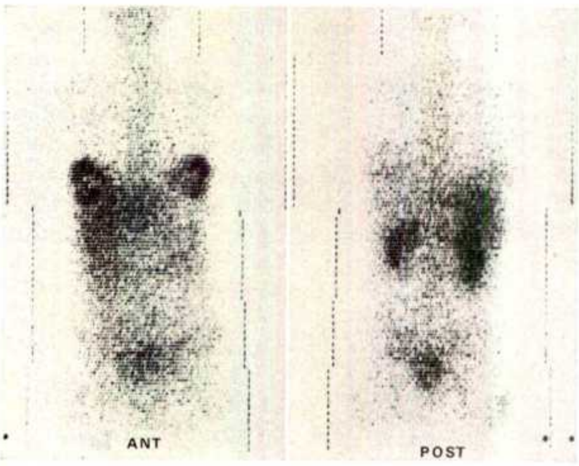

FIG. 1.

^{67}Ga whole-body scan showing uptake in both breasts and both kidneys.

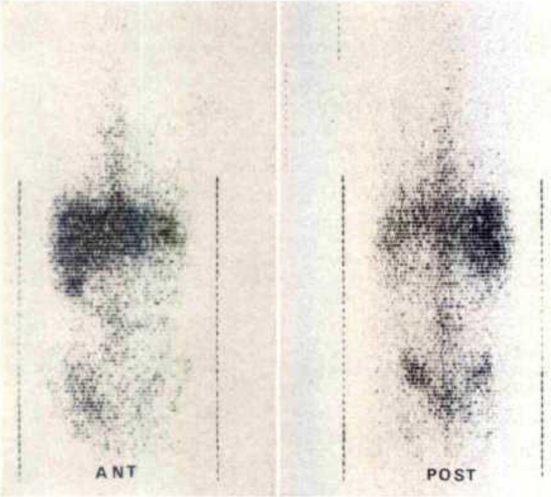

FIG. 2.

^{67}Ga whole-body scan four months later. No breast or kidney uptake. Activity noted in the region of the hepatic and splenic flexures.

been described as a "normal variant", but is particularly noted post-partum and in pregnancy (Larson and Schall, 1971; Gelrud and Arseneau, 1973; and Milder, 1973) which are classical "hyperprolactinaemic" states. However, prolactin levels were not reported by these authors.

Hyperprolactinaemia can occur in a wide variety of situations (Daughaday, 1974; Frieson and Hwang, 1973) including pituitary adenomas, primary hypothyroidism, chest wall injuries, carcinoma of the lung secreting ectopic prolactin, emotional and physical stress, advanced renal failure and many drugs, particularly Reserpine, Aldomet, oral contraceptives, tricyclic antidepressants, phenothiazines, and especially Maxolon (metaclopromide), which is one of the most potent prolactin stimulators. The patient reported here had received three such drugs, Stemetil, Largactil, and Maxolon, to combat nausea and vomiting. She was also just recovering from severe renal failure at the time.

It is entirely possible that the "normal variant" breast uptake of ^{67}Ga may, in fact, occasionally represent the manifestation of hyperprolactinaemia due to commonly-used drugs, such as anti-ovulatory, anti-hypertensive, anti-depressant and anti-nausea preparations. The last two are particularly pertinent to patients with neoplastic disease where ^{76}Ga scans find their greatest applicability. It is suggested that a serum prolactin level (either basal, or after TRH stimulation) in such "normal variants" would clearly establish whether hyperprolactinaemia was the cause of this incidental finding.

More important, using total body ^{67}Ga scans in breast-feeding mothers may expose the baby to harmful radiation either through drinking "hot" milk (Larson and Schall, 1971), or through close proximity to a "hot" breast. Clearly, this should be avoided.

ACKNOWLEDGMENT

We wish to thank Miss J. Latham for secretarial assistance.

A.V.S. is supported by a salary from the Endowment Fund administered by the Special Trustees of Guy's Hospital.

We are grateful to Dr. M. O. Thorner of St. Bartholomew's Hospital for the prolactin measurements and for his advice, and to Dr. M. McMillan and Miss H. Puxley of the Lewisham Group Laboratory, Lewisham Hospital, for performing TSH assays.

REFERENCES

DAUGHADAY, W. H., 1974. The adenohypophysis. In *Textbook of Endocrinology*, ed. R. H. Williams, p. 49 (W. B. Saunders Co., Philadelphia).

FRIESEN, H., and HWANG, P., 1973. Human prolactin. *Annual Review of Medicine*, *24*, 251–270.

GELRUD, L. G., and ARSENEAU, J. C., 1973. Metabolism (of ^{67}Ga). In *Atlas of Gallium-67 Scintigraphy*, ed. G. S. Johnston and A. E. Jones, pp. 7–10. (Plenum Press, New York).

LARSON, S. M., and SCHALL, G. L., 1971. Gallium-67 concentration in human breast milk. *Journal of the American Medical Association*, *218*, 257.

LARSON, S. M., MILDER, M. S., and JOHNSTON, G. S., 1973. Interpretation of the ^{67}Ga photoscan. *Journal of Nuclear Medicine*, *14*, 208–214.

MILDER, M. S., 1973. Scintigraphic interpretation (of ^{67}Ga). In *Atlas of Gallium-67 Scintigraphy*, ed. G. S. Johnston and A. E. Jones, pp. 11–29 (Plenum Press, New York).

1975, *British Journal of Radiology*, *49*, 381–382 APRIL 1976

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

MUST RADIOLOGISTS DO ALL THE REPORTING?

As a member of a quality survey team for the American College of Radiology, I find that some of your correspondents' complaint about radiologists not being present when they are needed is rather universal throughout the United States, especially during nights and week-ends. In very busy hospital centres this should be changed for the future so that a qualified radiologist is rotated through the night and weekend hours. However, Dr. Emrys-Roberts is chiefly concerned with small stations which have either no radiologists or only an occasional one and, therefore, the following two suggestions are more appropriate.

Especially since I value very highly the clinical examination of a radiologic patient, I think that the clinician should very definitely be allowed and encouraged to read films and put his opinion on the patient's chart. When feasible this could well be followed by a radiologist's reading. But, where the institution cannot afford or secure a radiologist the institution and the governing bodies must recognize that they do as best they can, hopefully with as qualified a person reading the films as is possible. We are all familiar with the fact that most qualified specialists prefer to read their films at any rate, perhaps disregarding the reading of the radiologist.

As opposed to regulations of our Society of Technologists, I have always encouraged our radiographers to learn as much as possible about physical as well as radiologic examination and diagnosis and to use this knowledge when I am absent. Our radiographers are competent to diagnose perhaps 80–90 per cent of our chests, 95 per cent of our bones and perhaps 50 per cent of our brain examinations. However, if your Dr. Emrys-Roberts has no radiologists available or one available only on great occasion, there is no possibility for such teaching, and our plan is of little use.

One last suggestion for such isolated or deprived hospitals is that they be supplied with a combination telephone and television connection with a centre supplied regularly with radiologists, so that virtually instantaneous interpretation can be secured. This is already a reality in electrocardiography diagnosis and in portions of our rural and Indian health services.

Yours, etc.,
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THE EDITOR—SIR,

THE ORGAN DISTRIBUTION OF ^{131}I-TYROSYL SOMATOSTATIN

Recently, Somatostatin (SRIF), a tetradecapeptide of hypothalamic origin, has evoked considerable interest because it can inhibit both insulin and pancreatic glucagon in concentrations somewhat greater than those required to inhibit growth hormone releasing factor (Alberti *et al.*, 1973; Koerker *et al.*, 1974). It has been suggested that SRIF may be used in conjunction with insulin in the treatment of the diabetic patient (Gerich *et al.*, 1974). Radio-iodination of SRIF is feasible because a tyrosyl group can easily be added to the molecule with retention of 50 per cent of biological activity (Guillermin, personal communication). This letter is a preliminary report of the distribution of ^{131}I-tyrosyl Somatostatin in the abdominal organs with particular focus upon the pancreas.

Tyrosyl-SRIF* was labelled with ^{131}I by means of the Hunter-Greenwood method using Chloramine-T. The specific activity achieved was 1·0–1·5 mCi/8–10 μg ^{131}I-tyrosyl-SRIF. The free iodine (as Na^{131}I) was less than 2 per cent. Four experiments were done using adult mongrel dogs with and without simultaneous administration of 600–1,000 μg of cold tyrosyl-SRIF. Serial scintigrams were then taken with the Pho Gamma III HP scintillation camera at five to ten minute intervals over a period of one to two hours. At that time, the dog was sacrificed and preparation for organ counts was performed within 30 minutes. The organ distribution data are presented in Table I.

In the three animals which were given carrier SRIF, there was scintigraphic evidence of an area of increased uptake superior to the kidney but distinct from the liver (Fig. 1). The dog that was given carrier-free SRIF failed to show any preferential concentration of radioactivity. Scans of the isolated, preserved stomach and thyroid performed four days after sacrifice showed diffuse uptake in these organs.

The distribution data and the scans taken have shown that ^{131}I-tyrosyl-SRIF does not selectively localize in the

TABLE I

DISTRIBUTION OF UPTAKE OF ^{131}I-TYROSYL-SRIF IN ABDOMINAL ORGANS

	Single injection experiment		Continuous infusion experiment	
Tissue	cpm/g	% dose/g	cpm/g	% dose/g
Pancreas	5,320	0·0006	6,174	0·0007
Liver	24,400	0·0019	9,548	0·0011
Spleen	29,800	0·0024	7,142	0·0008
Kidney	64,180	0·0050	79,132	0·0089
Whole blood	20,200	0·0016	10,581	0·0012

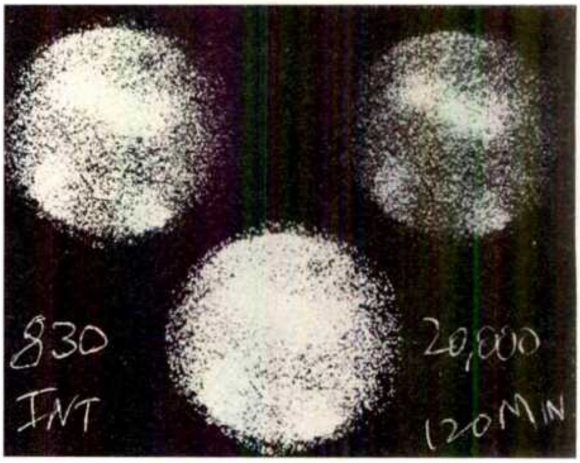

FIG. 1.

An antero-posterior scintigram of the abdomen showing an area of increased uptake superior to the upper poles of both kidneys.

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*Tyrosyl-SRIF was kindly supplied by Dr. D. H. Coy of the VA Hospital, New Orleans, Louisiana.

1976, *British Journal of Radiology*, *49*, 382–383

pancreas in spite of its inhibiting effect on pancreatic glucagon and insulin. If there had been concentration in the pancreas, one would have expected this to have occurred within the five-minute biological half-life of Somatostatin.

The kidney appears to be the principal route of elimination. The characteristics of short biological half-time and the preferential excretion through the kidneys are shared by many other biologically active peptides.

The coincident disappearance of activity in the inferior vena cava and the liver as well as the similar ranges of the hepatic and the whole blood concentration in Table I suggest that SRIF uptake in the liver is merely a reflection of blood pool. This is in accord with a previous report on the distribution of ^{131}I-tyrosyl-SRIF (Reading and Coy, 1973).

There are several reasons for the observed gastric activity. The uptake of the labelled SRIF appeared to be limited to the pyloric region. Somatostatin infusion has been shown to depress the serum gastrin in man and the site of radiopharmaceutical localization in our studies could have been the pyloric antrum (Bloom *et al.*, 1974).

Another possibility is that the diffuse uptake in the stomach and the thyroid was either free radioiodine or a labelled breakdown product of Somatostatin. While this explanation is consistent with the rapid biological half-life of SRIF and the appearance of the gastric and thyroid scans, it is subject to question. The image of the post-mortem stomach seen on the scan was heterogeneous and non-uniform and could have been due to autolysis which can occur unless strict precautions are observed as to the time of fixing and examination after defrosting of specimens.

Further observations will be necessary to confirm which of these two alternatives is true. If labelled Somatostatin does indeed localize in the antrum, it offers the intriguing possibility of specifically imaging the retained gastric antrum, a complication which may occur following gastroenterostomy.

Although one would have anticipated that the absence of a loading dose of SRIF would have increased the uptake in a target organ, the reverse of this was true in our experiments. In the absence of cold SRIF, there was no apparent visualization of stomach while this localization did occur when cold SRIF was used. In addition, the route of administration did not cause any major differences in the results except for a slower time course when the tyrosyl-SRIF was given by infusion.

^{131}I-tyrosyl Somatostatin does not localize in the pancreas after systemic administration. It is eliminated at a relatively rapid rate through the kidneys and its metabolic breakdown products concentrate to some extent in the stomach and the thyroid.

Yours, etc.,
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REFERENCES

Alberti, K. G. M. M., Christensen, S. E., Iversen, J., Seyer-Hansen, K., Christensen, N. J., Hansen, A. P., Lundbaek, K., and Orskov, H., 1973. Inhibition of insulin secretion by somatostatin. *Lancet*, *2*, 1299–1301.

Bloom, S. R., Mortimer, C. H., Thorner, M. O., Besser, G. M., Hall, R., Gomez-Pan, A., Roy, V. M., Russel, R. C. G., Coy, D. H., Kastin, A. J., and Schally, A. V., 1974. Inhibition of gastrin and gastric secretion by growth hormone release-inhibiting hormone. *Lancet*, *2*, 1106–1109.

Gerich, J. E., Lorenzi, M. V., Schneider, V., Karam, J. H., Rivier, J., Guillemin, R., and Forsham, P. H., 1974. Effects of somatostatin on plasma glucose and glucagon levels in human diabetes mellitus. *New England Journal of Medicine*, *291*, 544–547.

Koerker, D. J., Ruch, W., Chideckel, E., Palmer, J., Goodner, C. J., Ensinck, T., and Gale, C. C., 1974. Somatostatin: Hypothalamic inhibitor of the endocrine pancreas. *Science*, *184*, 482–484.

Redding, T. W., and Coy, D. H., 1973. The disappearance, distribution, and excretion of ^{125}I-labeled tyrosine-1-tyr.-1-GIF) in mice, rats, and man. Abstract. Endocrine Society Fifty Sixth Meeting.

The Editor—Sir,

Effect of Stress on Blood Perfusion and Vascular Space in Transplanted Mouse Tumours

In recent years there have appeared in the literature several reports relating to the effects of irradiation on various vascular parameters (blood flow, blood volumes, etc.) in transplanted animal tumours. In most cases irradiation was carried out under anaesthesia (McAlister and Margulis, 1963; Song and Levitt, 1971; Song *et al.*, 1972), and we have recently shown that the two most commonly used anaesthetics, pentobarbitone sodium (Nembutal) and urethane, greatly increase relative blood perfusion in five types of transplanted mouse tumours (Zanelli *et al.*, 1975).

The vascular bed is very sensitive to stress. Exposure to hot and cold environments, for instance, has been shown to affect cardiac output, blood pressure and tissue blood flow, and to alter the pattern of blood perfusion among the various tissues of the body (Hales, 1973; Alexander *et al.*, 1973). As a preliminary to a study of the effects of irradiation on tumour blood perfusion and vascular space by means of ^{86}Rb and ^{125}I-human serum albumin (^{125}I-HSA) in non-anaesthetized mice, we investigated the effects of immobilization of the mice on the above parameters.

Three types of tumours have been investigated in two strains of mice: a carcinoma "NT" in CBA male mice (volume doubling time 3·0 days), a sarcoma "F" in male CBA mice (volume doubling time 1·5 days) and a sarcoma "2" in WH male mice (volume doubling time 3·7 days). The tumours were obtained by implanting approximately 1 mm^3 of tumour tissue subcutaneously on the chest wall. Sham irradiations were carried out by the standard procedure which is usually followed in our laboratory for irradiation of tumours in anaesthetized mice. The mice were placed in the holder five to ten minutes before the start of irradiation which may last for up to 10–15 minutes. For the present purposes a total immobilization time of 20 minutes was chosen. Groups of mice were then sacrificed at various intervals up to 48 hours later. Mice which had remained untouched up to the time of tracer injection served as controls. All the mice in a given experiment were sacrificed on the same day to avoid differences in tumour size, particularly among the fast-growing tumours (Sarcoma "F").

The techniques for measuring relative blood perfusion and vascular space have been described (Zanelli and Fowler, 1974). Briefly, ^{86}Rb and ^{125}I-HSA (Radiochemical Centre, Amersham, England) were diluted in physiological saline to obtain a solution containing approximately 2·5 μCi of ^{86} Rb and 0·25 μCi of ^{125}I-HSA in 0·1 ml. Exactly 0·1 ml. was then injected quickly into the tail vein of the (non-anaesthetized) mice. One minute later the animals were killed by cervical dislocation and decapitation, and blood, tumour, tail and skeletal muscle from the upper hind legs (as representative of a normal tissue) were collected, placed in pre-weighed glass vials, weighed and counted in a two channel autogamma counter (Wallach Instruments Ltd., Theale, Berkshire) along with standards of the injection solution and of the two isotopes used. Any mouse with more than 15 per cent ^{86}Rb in the tail was assumed to represent a technically poor injection and was rejected from the calculations. The average ^{86}Rb in the tail of the animals included in the calculations was less than 3 per cent of the injected activity. *Relative* blood perfusion was calculated as the percentage of the injected ^{86}Rb taken up/g by tumour or muscle. Vascular space was calculated from (^{125}I counts/unit time/g of tissue)/(^{125}I counts/unit time/g of blood).

The results, shown in Figs. 1 and 2, show that stress does, in most cases, influence relative tumour blood perfusion (Fig. 1) and vascular space (Fig. 2). In these figures the first set of points (those before zero hours) are for the "untouched" controls and those points which are significantly different from the controls ($p \leqslant 0{\cdot}05$) are denoted by *S*. In tumours, both parameters are still depressed 48 hours after sham irradiation. In muscle, on the other hand, only one result shows a significant change (carcinoma "NT" in CBA mice at 48 hours) from the control values (Fig. 1). This points to a fundamental difference in the response to stress between the normal vasculature and that of transplanted tumours, and tends to support the view expressed by Cater *et al.* (1962) that the vasculature of tumours is easily affected by changes in systemic blood pressure since immobilization is very likely to bring about such changes.

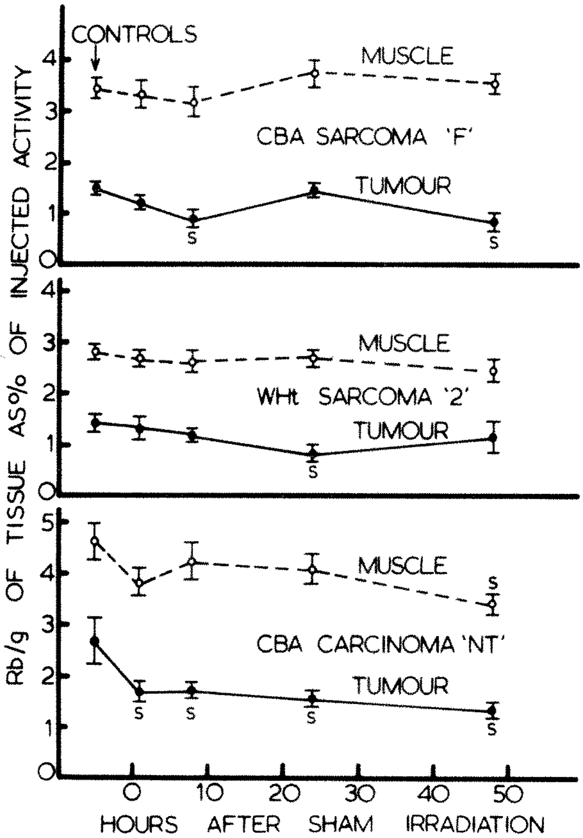

FIG. 1.

^{86}Rb uptake/g of tumour and muscle as a function of time after sham-irradiations. The bars show the standard deviation and *S* denotes those points which are significantly different from the controls ($p \leqslant 0{\cdot}05$).

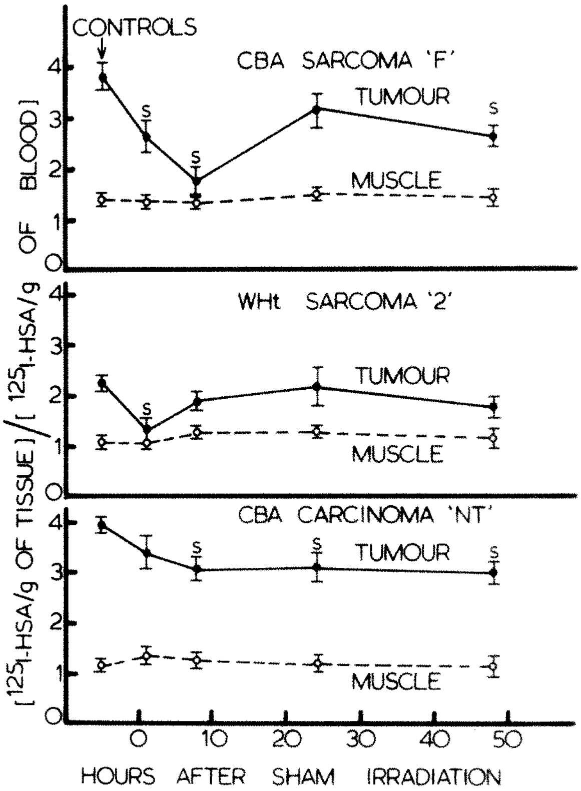

FIG. 2.

^{125}I-human serum Albumin vascular space in tumour and muscle as a function of time after sham-irradiation. The bars show the standard deviation and *S* denotes those points which are significantly different from the controls ($p \leqslant 0{\cdot}05$).

From the practical point of view, the above results, together with those regarding the effects of anaesthetics (Zanelli *et al.*, 1975) mean that investigations (at least by means of radioactive tracers) into the *immediate* effects of irradiation upon the vasculature of experimental tumours, and any results which depend upon blood flow in experimental tumours are likely to be unreliable for one of two reasons. If the mice are anaesthetized by means of Nembutal or urethane, a redistribution of the cardiac output takes place in favour of the tumour. If, on the other hand, the animals are immobilized for long periods of time without anaesthetics, the present findings suggest that protracted and severe tumour ischaemia may occur. In either case, these procedures can affect the results of experiments which depend on tumour oxygenation.

The authors would like to express their gratitude to Dr. J. F. Fowler and Dr. Juliana Denekamp for their advice and productive discussions.

Yours, etc.,
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REFERENCES

ALEXANDER, G., BELL, A. W., and HALES, J. R. S., 1973.

1976, *British Journal of Radiology*, *49*, 384–386

Correspondence

Effect of cold exposure on tissue blood flow in the newborn lamb. *Journal of Physiology*, *234*, 65–77.

CATER, D. B., GRIGSON, C. M. B., and WATKINSON, D. A., 1962. Changes of oxygen tension in tumours induced by vasoconstrictor and vasodilator drugs. *Acta Radiologica*, *58*, 401–431.

HALES, J. R. S., 1973. Effect of exposure to hot environments on the regional distribution of blood flow and on cardiorespiratory function in sheep. *Pflugers Archiv*, *344*, 133–148.

McALISTER, W. H., and MARGULIS, A. R., 1963. Angiography of malignant tumours in mice following irradiation. *British Journal of Radiology*, *81*, 664–675.

SONG, C. E., and LEVITT, S. H., 1971. Vascular changes in Walker 256 carcinoma of rats following X-irradiation. *Radiology*, *100*, 397–407.

SONG, C. W., PAYNE, J. T., and LEVITT, S. H., 1972. Vascularity and blood flow in X-irradiated Walker Carcinoma 256 of rats. *Radiology*, *104*, 693–697.

ZANELLI, G. D., and FOWLER, J. F., 1974. The measurement of blood perfusion in experimental tumours by uptake of ^{86}Rb. *Cancer Research*, *34*, 1451–1456.

ZANELLI, G. D., LUCAS, P. B., and FOWLER, J. F., 1975. The effects of anaesthetics on blood perfusion in transplanted mouse tumours. *British Journal of Cancer*, *32*, 380–390.

THE EDITOR—SIR,

RADIATION PROTECTION AND PHARMACEUTICAL REQUIREMENTS

The basis of Mr. Moore's concern (Moore, 1975) seems to lie in his assumption that pharmaceutical requirements for intravenous injections are more important than radiological protection from airborne activity. If this is accepted, then presumably "substantial sums" will be spent by the National Health Service on installing lamina air flow cabinets in all radiopharmacies. These cabinets can be obtained with a balanced downflow system; if the exhaust is part recirculated within the cabinet and part extracted through a duct to the outside of the building (Smith, 1975) then both sides of the argument seem to be satisfied.

In radioisotope laboratories used only for *in-vitro* and research work fume-cupboards are necessary, not just for "exceptionally hazardous" procedures, but for most radioisotope work. To quote one particular instance, a technician who was labelling hormones with ^{125}I was found to have accumulated 0·5 μCi ^{125}I in his thyroid (Drolc, 1973), but when an efficient fume-cupboard was used, his thyroid burden became negligible.

Regular surveys of laboratories using radioisotopes in at least this part of the country show without doubt that spills are certainly not infrequent.

In reality the Code of Practice (1972) seems modest in its requirements and when applied to individual situations its recommendations are usually satisfied without great expense.

Yours, etc.,
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REFERENCES

Code of Practice for the Protection of Persons against Ionising Radiations arising from Medical & Dental Use, 1972 (Her Majesty's Stationery Office, London).

DROLC, Z., 1973. Personal communication.

MOORE, R. D., 1975. Containment of unsealed sources of radionuclides in hospitals. *British Journal of Radiology*, *48*, 410.

SMITH, P. H. S., 1975. Personal communication.

THE EDITOR—SIR,

USE OF CRE INSTEAD OF TDF

The nominal standard dose concept proposed by Ellis (1967) for comparison of various treatment regimes has been widely accepted. The nominal standard dose is associated with treatment schedules which lead to full tolerance of tissue. Using this idea, Kirk *et al.* (1971) have proposed the use of Cumulative Radiation Effects (CRE) at the partial tolerance level. Orton and Ellis (1973) have proposed time, dose, fractionation factors for dealing with treatment schedules leading up to and including tolerance. A question, therefore, arises which of these two concepts should be used for dealing with problems of radiotherapy at the present juncture.

While propounding the NSD concept, Ellis has cautioned that continuous testing and sifting of data are desirable to verify the concept and to adjust the exponents of N and T in the NSD equation

$$\mathrm{NSD} = DN^{-J}T^{-H} \quad . \quad . \quad . \quad . \quad (1)$$

with initial values of 0·24 and 0·11 for J and H respectively. Results of a few investigations have recently been published which indicate the possibility of change in the values of these exponents J and H. Fowler (1971) felt that exponent J should be slightly larger than 0·24 and H should be slightly less than 0·11. The data of Berry *et al.* (1974) matched with a total exponent, $J+H$, of 0·46 in place of 0·35. The data of Dutriex *et al.* (1973) on human skin indicated a value of $H=0{\cdot}22$. Liversage (1971) was also of the opinion that this exponent should be larger. Loeffler (1974) has found that the present exponents are not consistent with his clinical data. Phillips and Ross (1974) found that their data on mouse oesophagus were more consistent with values of J and H of 0·28 and 0·05 respectively. It is apparent from this that the values of J and H are at present not fixed and have to be arrived at only after accumulation of enough data from clinical investigations.

It can be easily shown that $(\mathrm{CRE})^{\frac{1}{1-J-H}} = \mathrm{TDF} \times 10^3$

TDF is the time, dose and fractionation factor. For values of $J=0{\cdot}24$ and $H=0{\cdot}11$, the exponent of CRE becomes

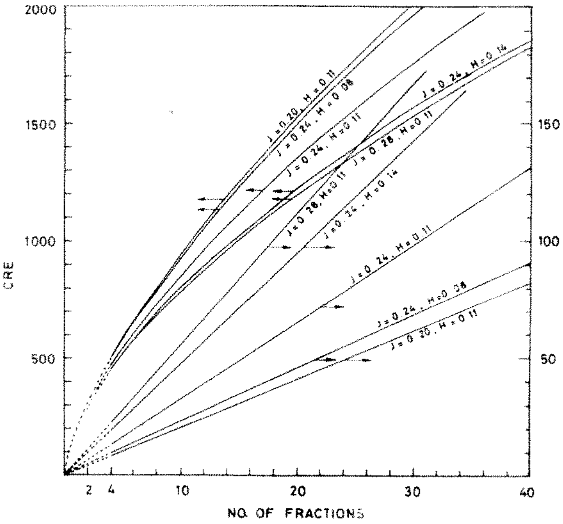

FIG. 1.

Variations in CRE with number of fractions, shown by curves for 200 rad per fraction delivered five times a week for values of $J=0{\cdot}28$, 0·24 and 0·20 and $H=0{\cdot}08$, 0·11 and 0·14. Straight lines indicate the corresponding variation in TDF. CRE is not additive due to the curvilinear nature of the graph while TDF is additive.

1·538. This shows that the TDF values will be affected to a much larger extent by variation of the values of J and H.

The effect of changes of exponents on the magnitude of CRE and TDF was studied. For a given dose of 200 rad/fraction, the variation in CRE is presented in Fig. 1, for $J=0{\cdot}24$, $0{\cdot}28$ and $0{\cdot}20$ with $H=0{\cdot}11$ and for values of $H=0{\cdot}08$, $0{\cdot}11$, $0{\cdot}14$ for values of $J=0{\cdot}24$. The values of TDF for these exponents are also shown in the same figure. It can be seen from this graph that for 30 fractions of 200 rad/fraction the NSD is changed by about ±14 per cent with a change of 0·04 in the value of J and ±10 per cent with a change of 0·03 in the value of H. The corresponding changes of TDF are 67 per cent and 38 per cent. It may further be noted that when the exponent of J is changed by 0·04 the changes in TDF are not equal when the magnitude is increased or decreased. It is, therefore, our opinion that use

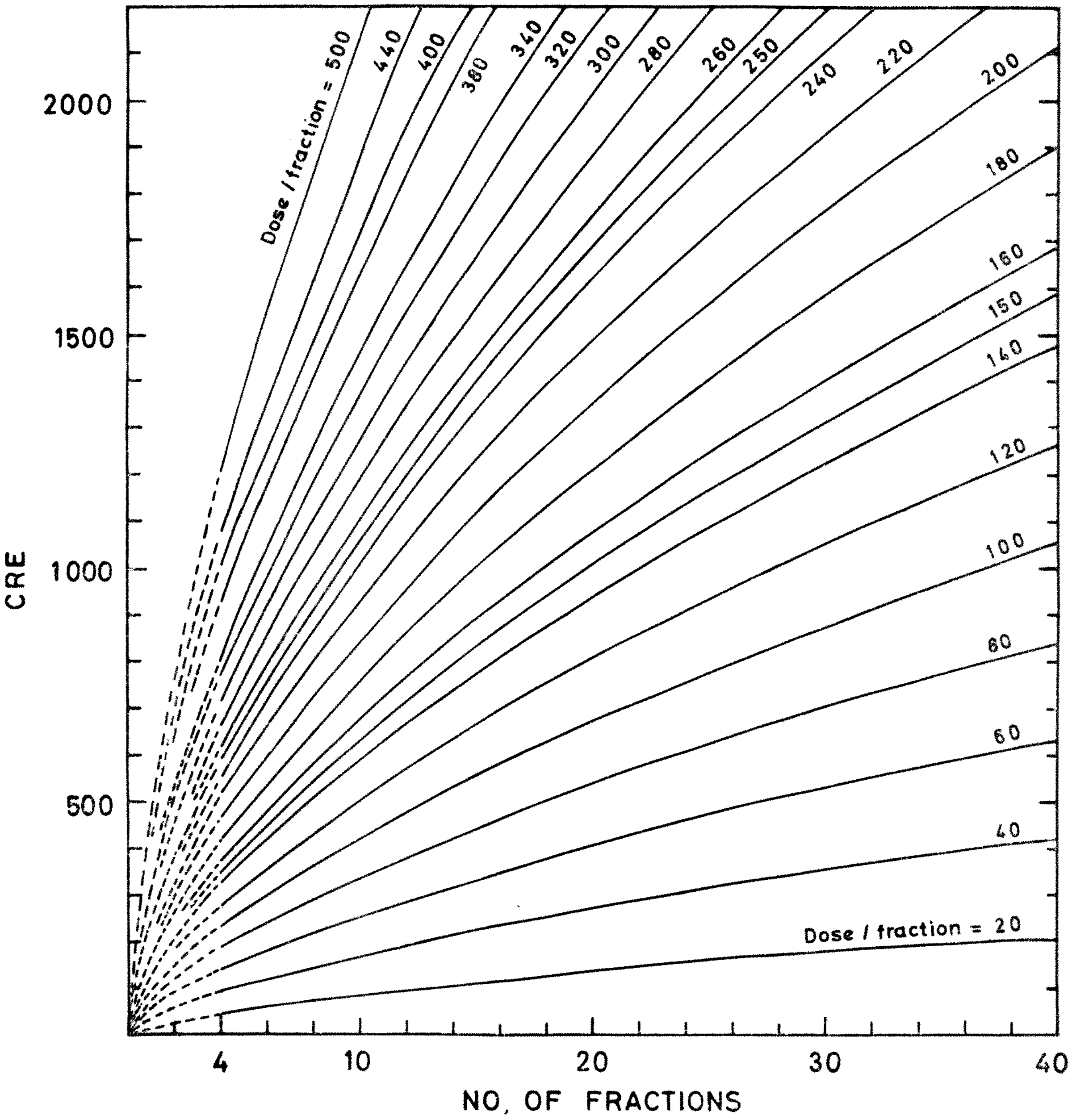

FIG. 2.

Variation in CRE with number of fractions for various values of dose per fraction delivered five times a week for $J=0{\cdot}24$ and $H=0{\cdot}11$.

of TDF is not to be advocated at the present juncture because of its greater dependence on variations in the exponents of T and N.

Orton and Ellis (1973) have pointed out that the NSD concept has been misunderstood and incorrectly used in many cases. The use of TDF is very easy because of its additivity and as values are readily available in tabular form. Simplification in the use of CRE could be achieved to a certain extent if CRE values were readily available and did not need to be evaluated each time. CRE values for various given doses and fractions were evaluated for one fraction/week to five fractions/week. Data for five fractions/week are presented in Fig. 2. Use of this graph is illustrated by an example.

Example

A patient is given a treatment of ten fractions of 200 rads a day in two weeks, the total intended number of fractions being 30. After a gap of five days, the treatment is resumed and it is desired that the treatment should be completed in another ten fractions. What should be the daily dose to obtain the effect initially intended?

Solution

From Fig. 2 the expected NSD for 30 fractions of 200 rads per day = 1,760 ret.
CRE for ten fractions of 200 rads = 855 reu.
Correction due to gap of five days: $\left(\frac{14}{14+5}\right)^{\cdot 11} = 0{\cdot}97$
Residual CRE = 855 × 0·97 = 829·5 reu.
CRE of 829 reu is given by:
  4·3 fractions of 340 rad/fraction.
  4·6 fractions of 320 rad/fraction.
  5·1 fractions of 300 rad/fraction.
NSD of 1,760 ret is given by:
  13·4 fractions of 340 rad/fraction.
  14·6 fractions of 320 rad/fraction.
  16·4 fractions of 300 rad/fraction.
it is apparent now that a daily dose of 320 rad should be used if an additional ten fractions are to give the total NSD of 1,760 ret. We wish to thank Dr. F. Ellis for stimulating discussions on this subject during his visit to India.

Yours, etc.,
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REFERENCES

BERRY, R. J., WIERNIK, G., PATTERSON, T. J. S., and HOPEWELL, J. W., 1974. Excess late subcutaneous fibrosis after irradiation of pig skin consequent upon the application of the NSD formula. *British Journal of Radiology*, *47*, 277–281.

DUTREIX, J., WAMBERSIE, A., and BOUNIK, C., 1973. Cellular recovery in human skin reactions: application to dose fraction number over all time relationship in radiotherapy. *European Journal of Cancer*, *9*, 159–167.

ELLIS, F., 1967. Fractionation in radiotherapy. In *Modern Trends in Radiotherapy*. Eds. Deeley and Wood, *1*, 34–51.

FOWLER, J. F., 1971. Experimental animal results relating to time-dose relationships in radiotherapy and the "ret" concept. *British Journal of Radiology*, *44*, 81–90.

KIRK, J., GRAY, W. M., and WATSON, E. R., 1971. Cumulative radiation effect. Part I: fractionated treatment regimes. *Clinical Radiology*, *22*, 145–155.

LIVERSAGE, W. E., 1971. A critical look at the ret. *British Journal of Radiology*, *44*, 91–100.

LOEFFLER, R. K., 1974. Influence of fractionation on acute and late reactions in vocal cord carcinoma. *American Journal of Roentgenology and Radium Therapy*, *121*, 748–753.

ORTON, C. G., and ELLIS, F., 1973. A simplification in the use of the NSD concept in practical radiotherapy. *British Journal of Radiology*, *46*, 529–537.

PHILLIPS, T. L., and ROSS, G., 1974. Time dose relationships in the mouse esophagus. *Radiology*, *113*, 435–440.

THE EDITOR—SIR,

CONTAINMENT OF UNSEALED SOURCES OF RADIONUCLIDES IN HOSPITALS

Since my return from abroad, I have seen the letter by Mr. Moore (1975) on the containment of unsealed sources of radionuclides in hospitals. His letter was prompted by my paper (Hughes, 1974) on the design of efficient fume-cupboards which took as its starting point the need for a fume-cupboard and then proceeded to describe the necessary design details.

I agree with Mr. Moore that there are many situations where the provision of a fume-cupboard is an inappropriate and expensive method of providing containment for unsealed sources. We have recognized this fact at Leeds and in some of our laboratories have introduced less elaborate dispensing cabinets for non-sterile work (Holliday, Fielding, and Hocking Ltd.*). These are similar in construction to a simple glove-box but with open ports or a restricted aperture for access. They can be adequately ventilated by a low capacity and less expensive extraction system than that required for a fume-cupboard, and provide sufficient containment and localization for many procedures.

If sterility of the unsealed source has to be maintained in addition to protecting the operator, quite elaborate cabinets and ventilation equipment may be needed (Everett and Hughes, 1975). The requirements for such work are discussed in the "Guidelines for the preparation of radiopharmaceuticals in hospitals" which was drafted by a working party following the seminar held on this topic at the Royal Marsden Hospital, Sutton, in October 1974 and appeared as *B.I.R. Special Report No. 11* (1975).

Yours, etc.,
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REFERENCES

EVERETT, K., and HUGHES, D., 1975. *A Guide to Laboratory Design* (Butterworth, London).

HUGHES, D., 1974. Clean rooms. *Chemistry in Britain*, *10*, 84–87.

1974b. The design and installation of efficient fume-cupboards. *British Journal of Radiology*, *47*, 888–892.

MOORE, R. D., 1975. Containment of unsealed sources of radionuclides in hospitals. *British Journal of Radiology*, *48*, 410.

Special Report No. 11, 1975. *Guidelines for the Preparation of Radiopharmaceuticals in Hospitals* (British Institute of Radiology).

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*Holliday, Fielding and Hocking Ltd., Wesley Works, Wesley Place, Leeds LS9 8HA.

1976, *British Journal of Radiology*, *49*, 387–388 ABRIL 1976

Statement of Co-operation

The British Institute of Radiology and The Royal College of Radiologists

The Royal College of Radiologists and The British Institute of Radiology have each a distinct role to play in British radiology, and believing that these roles should be complementary rather than competitive, have prepared the present document for circulation to all their members. Its purpose is to define those areas of common interest where close co-operation between the two bodies is desirable and to indicate ways of achieving this.

Their separate roles stem chiefly from their differing terms of membership. The British Institute of Radiology from its foundation as the Röntgen Society in 1897 has admitted medical, scientific and industrial members on entirely equal terms and draws its strength from the broad spectrum of knowledge and experience which this wide membership brings to the furtherance of the theory and practice of radiology and its allied sciences.

The Faculty of Radiologists was founded in 1939 as an exclusively medical body to represent the interests of medical radiologists on professional matters and to establish high standards of training and qualification for entry to the profession. Its recent elevation to the Status of a Royal College naturally adds weight and authority to it in this role.

The role of the Royal College will be to continue to encourage the clinical practice of radiology and to liase on clinical matters with the other Royal Colleges, Faculties and Clinical Societies. As the professional body for medical radiologists it will have representatives on the Joint Consultants Committee for England and Wales and for Scotland, the Councils for Postgraduate Medical Education for England and Wales and for Scotland, and the Distinction Awards Committee. It will conduct negotiations for medical radiologists on professional matters with the Department of Health and will continue to nominate assessors to Advisory Appointments Committees for consultant appointments in radiodiagnosis, radiotherapy, and nuclear medicine. It will continue to organize scientific meetings concerned with the clinical practice of radiodiagnosis and radiotherapy in liaison with The British Institute of Radiology; to arrange its named lectures; to grant scholarships to radiologists in this country and from overseas for the furtherance of their experience and to organize postgraduate courses in radiodiagnosis, radiotherapy, nuclear medicine and ultrasound; to send its Travelling Professors overseas to developing countries and to conduct professional examinations for the Fellowship of the Royal College of Radiologists (F.R.C.R.). It will continue to publish its journal CLINICAL RADIOLOGY and to promote research. Through its Regional Postgraduate Education Advisers it will continue to encourage recruitment to both branches of radiology and to supervise the training of radiologists.

The Institute sees its main function to be the promotion and dissemination of scientific and medical knowledge in all fields of diagnostic and therapeautic radiology and the allied sciences. This aim will be pursued in the future, as in the past, by its programme of meetings covering all aspects of radiology and often crossing disciplinary boundaries, both medical and non-medical; by its organization of provincial and overseas branches; by its encouragement of research in radiology and in those newer fields of investigation such as radiobiology, ultrasound and nuclear medicine; by setting up working parties and organizing clinical trials in which both medical and non-medical scientists may be involved; and pre-eminently by its publication of the BRITISH JOURNAL OF RADIOLOGY and its Supplements.

Once these roles are recognized it is clear that most medical radiologists will wish in future, as in the past, to participate as members in the activities of both bodies. There are naturally areas of common interest where close collaboration between the Institute and the Royal College is desirable in order to serve their members and British radiology as a whole in the most efficient and economical manner. Some ways of achieving this collaboration are set out below: others will doubtless arise in the future.

MECHANISM OF CO-OPERATION

General

The Institute and the Royal College *together* constitute the National Radiological Body recognized by international radiological organizations such as the European Association of Radiology and the International Society of Radiology. For this and similar reasons regular liaison exists and will be extended between the Secretary of the Royal College and the General Secretary of the Institute, and between the Registrar of the Royal College and the Honorary Secretaries of the Institute.

Scientific meetings

The programme of scientific meetings organized by the Institute and the Royal College and the Radiology Section of the Royal Society of Medicine will continue to be co-ordinated as in the past. While all three bodies will retain full responsibility for the particular meetings they each organize, including their memorial lectures, this joint planning of the programme has operated to the great advantage of all their members and it serves as a model for co-operation in other areas.

Liaison between committees

To improve liaison cross-representation is being arranged between the Faculty Boards of Radiodiagnosis and Radiotherapy and Oncology of the Royal College and the Medical Committee of the Institute.

Advice to Statutory authorities

In matters involving scientific and technical issues, *e.g.* codes of practice, the training of technicians, organizational matters within the National Health Service, participation in the International Committee on Radiation Protection (I.C.R.P.) the International Committee on Radiation Units (I.C.R.U.) and discussion on E.E.C. directives, the Institute and the Royal College may consider these issues separately or in joint working parties and may submit either separate or joint recommendations to the relevant authorities. They will, however, collaborate as closely as possible in such matters to prevent conflicting recommendations arising merely from inadequate liaison.

Publications

The journals of the two bodies and their other occasional publications will retain their separate identities and styles, but the possibility of combining some of the editorial office facilities will be explored in the interests of economy.

Accommodation

A previous attempt in the late 1960s to establish a British Radiology House which could accommodate both the Royal College and the Institute as separate bodies but in close enough proximity to allow them to share valuable facilities such as lecture theatre, The Royal College's film museum and the Institute's Library, was unsuccessful. The Royal College is at present seeking new accommodation and if the possibility were to arise of acquiring neighbouring properties suitable for separate occupation by the two bodies the Institute would consider whether it should move from its existing premises, convenient though they are for the present, to make possible the closer collaboration and sharing of facilities referred to above.

Conclusion

The purpose of these proposals is not primarily financial though the collaboration we aim at should bring some economies. Rather we see their main purpose as the recognition of complementary roles for The Royal College and the Institute and the agreement of both to collaborate closely in areas of overlapping interest to their mutual advantage and that of British radiology as a whole.

HOWARD MIDDLEMISS
Immediate Past-President
The Royal College
of Radiologists
May, 1975.

WALTER SHANKS
Immediate Past-President
The British Institute
of Radiology

Book reviews

Joint Diseases—All the Arthropathies. By E. C. Huskisson and F. Dudley Hart, pp. xiii+52, 2nd edn, 1975 (Bristol, John Wright and Sons), £3·25.

The second edition of this small handbook has been published just over a year after the first printing. This gives a good indication of the popularity and acceptance of the work. A few additions have been made, the most notable being a classification of the types of drugs used in rheumatic diseases and a separate section on back pain. There is a short synopsis of each condition with notes on the incidence, distribution, clinical pattern, associated features and complications, laboratory findings and treatment. Radiological features are very briefly enumerated but not illustrated. Despite this, radiological trainees will appreciate the format of the book as an aid to revision, especially in preparation for examinations containing multiple choice questions. I suspect that compilers of this form of inquisition will also appreciate this, but for different reasons!

W. M. PARK.

Real Solids and Radiation. By A. E. Hughes and D. Pooley, The Wykeham Science Series, pp. 196, 1975 (Wykeham Publications Ltd., London), £3·00.

This book would interest physicists who are concerned with the effects of radiation on materials and in particular with the defects produced by the interaction of electromagnetic and other radiations with solids. Medical readers will find some interest in the last chapter which contains a short section describing how radio-photo-luminescence and radio-thermo-luminescence come about. The authors, from the Atomic Energy Research Establishment at Harwell, are concerned respectively with the development and the physics of materials used in the atomic energy field.

They have succeeded in writing a book which describes how the properties of real solids, as distinct from idealized ones which are so often used in theoretical descriptions of solid-state behaviour, may be understood in terms of the atomic and electronic structure modified by the presence of various types of structural defect. The interaction of solids with radiation has however been kept in mind throughout the book and is a recurring theme. When discussing the effects of radiation, reference is made not only to the electromagnetic spectrum from infrared to high energy radiation (10 MeV), but also to ion bombardment, neutron irradiation, and electron irradiation.

The book provides a condensed, but nevertheless wide introduction to the physics of solids. The first two chapters, dealing with atoms and atomic structure, electron shells and types of crystal bonding, could well be of assistance to anyone teaching physics up to degree level. The descriptions given in the text of the properties of matter are sufficiently complete that the book can be read without necessarily following the mathematical treatment. Having said this, it is important also to say that wherever formulae and mathematical descriptions are useful or relevant to what is being said these have been included.

The book is very well written, and the diagrams and illustrations are of a high standard. It is a production which will appeal to those journal readers who wish to learn about the solid state from a very basic viewpoint. The production is in glossy paperback form and at the price is very good value.

N. W. RAMSEY.

Forthcoming events and other notices

The editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meetings announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

ANNUAL CONGRESS AND SCIENTIFIC EXHIBITION

To be held on April 8–9, 1976 at the University College, London. For information and registration please contact the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

RADIOLOGY OF VISCERAL VENOUS OBSTRUCTION

The Mackenzie Davidson Memorial Lecture, by Dr. M. Viamonte, Director of Radiology, University of Miami, School of Medicine, to be given at the University College, London, April 8, 1976.

INSTITUTE OF ACOUSTICS SPRING CONFERENCE 1976

To be held at Engineering and Science Building, Liverpool Polytechnic, Byrom Street, Liverpool 3, April 12–14, 1976.

Contributions are invited and should be submitted to Dr. R. Lawrence, Principal Lecturer, Acoustics Group, Physics Department, Liverpool Polytechnic.

Further information and registration from The Secretary, Institute of Acoustics, 47 Belgrave Square, London SW1X 8QX.

MEDICAL IMAGES: FORMATION, PERCEPTION AND MEASUREMENT

The Seventh L. H. Gray Conference, which will be concerned with the fundamentals of medical images, will be held at the University of Leeds, England, on April 13–15, 1976.

Address for further information: Dr. M. J. Day, Regional Medical Physics Department, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, England.

THE USE OF HYPERTHERMIA AND NON-IONIZING RADIATION IN THE TREATMENT OF CANCER, May 21, 1976

This meeting to be held at the British Institute of Radiology, Institute House, 32 Welbeck Street, London W1M 7PG.

Further information from the General Secretary.

POSTGRADUATE COURSE IN TOMOGRAPHY OF THE TEMPORAL BONE

To be held in Copenhagen, June 3–4, 1976. The course is sponsored by the I.C.R., the A.E.R. and the Scandinavian Association of Radiologists, and will be directed by Dr. Sam Brünner, president of the Congress.

For further information and registration, please contact Dr. Paul E. Andersen, Department of Radiology, University Hospital, 5000 Odense, Denmark.

HEALTH PHYSICS SUMMER SCHOOL

The 17th annual Summer School in Health Physics (Radiation Protection) will be held at Imperial College from June 21, to July 2, 1976.

Initial enquiries should be sent to Dr. H. D. Evans, Department of Chemical Engineering, Imperial College, London SW7 2AZ.

BREAST: NON-CANCEROUS DISEASES

To be held in Strasbourg, France, June 30–July 3, 1976. The 4th International symposium on Senology, under the auspices of the European Association of Radiology; includes study-groups with invited lectures and methods, mastopathies and lactation; proffered papers on topics covered by the above three study-groups and additionally; infections, malformations, breast pathology, computer analysis, comparative psychology and breast functions; a scientific exhibition and a technical exhibition.

The symposium will be preceded by postgraduate teach-ins, on June 28, 29, ultrasonography (by Société Française d'Echographie) on June 29, thermology (European Thermographic Association) and on June 29, xerography.

Apart from the postgraduate teach-ins, there will be simultaneous translation in the official languages of the symposium – English, French and German.

Further information from Symposium Sénologie 1976, Professor Charles Gros, Palais des Congrès, 67000 Strasbourg, France.

COMPUTERS IN RADIOTHERAPY IN EUROPE

It is proposed to hold a Workshop at IAEA, Vienna, on July 5–10, 1976, organized by the Groupe Informatique, A.E.R. with the support of the European Association of Radiology. The aim will be to establish the contribution that the computer makes at the clinical level in the fields of dose computation, clinical records, radiobiology, etc., and to determine future development.

Further information from Dr. D. N. Edwards, Clinical Research Unit, Mersey Regional Centre for Radiotherapy and Oncology, Clatterbridge Hospital, Bebington, Wirral, Merseyside L63 4JY, U.K.; or Dr. T. Moller, Radioterapikliniken, Lasarettet, S-221 85 Lund, Sweden.

FIRST MEETING OF THE WORLD FEDERATION OF ULTRASOUND IN MEDICINE AND BIOLOGY

This meeting, to be held August 3–7, 1976 in San Francisco is the third world congress on ultrasonics in medicine.

Reduced registration fees are payable by members of the international sub-group of the British Medical Ultrasonics Group.

Further information from: 1st W.F.U.M.B., PO Box 25606, Oklahoma City, Oklahoma 73125, U.S.A.

For information above B.M.U.G. contact the General Secretary, B.I.R., 32 Welbeck Street, London W1M 7PG.

8TH CONGRESS OF THE SOCIETY OF HUNGARIAN RADIOLOGISTS AND 12TH ANNUAL MEETING OF THE EUROPEAN SOCIETY FOR RADIATION BIOLOGY

To be held in Budapest, Hungary, October 19–22, 1976.

For further information please contact the Congress Office (H-1361 Budapest, PO Box 32, Hungary).

RADIATION PROTECTION: AN EXAMPLE OF ACTION AGAINST MODERN HAZARDS

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P. no. 33, 92260 Fontenay-aux-Roses, France.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colégio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Obituary

Professor R. A. Oliver

It is with regret that we advise readers of the death on Saturday, March 6, 1976, of Professor Ray Oliver (1921–1976) member of the British Institute of Radiology and an active member of many of its Committees.

We hope to publish a full obituary in the near future.

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Sir Charles Gairdner Hospital
Perth Medical Centre
PERTH, WESTERN AUSTRALIA

Radiologist

The Sir Charles Gairdner Hospital is a 540 bed general hospital in the process of expanding to 900 beds. The Radiology Department is presently well equipped and a new and enlarged department will be incorporated in a building presently under construction.

The department presently has an establishment of five specialists and four registrars. A general radiologist is required but a particular interest in ultrasound or neuroradiology may be an advantage.

Remuneration is partly by sessional payment and partly by a series of allowances. It should total not less than $40,000 per annum. Further information on conditions of service, provision of travel expenses and details of the hospital and the department are available on request from the Head of the Department. Applications close 30th April, 1976, and should be forwarded, together with the names and addresses of three referees, a recent photograph and curriculum vitae to the Medical Superintendent, Sir Charles Gairdner Hospital, Perth Medical Centre, Shenton Park, Western Australia, 6008

Staff Radiologist

Large Midwestern University needs Radiologist with interest in Ultrasound and/or C.T. Scanning. Present ultrasound facility expanding. C. T. scanner expected in mid-summer.
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Printed in Great Britain by Lund Humphries
London and Bradford
Published by THE BRITISH INSTITUTE OF RADIOLOGY
32 Welbeck Street, London W1M 7PG

ISSN 0005-1285

5.11.76

Volume 49 Number 58
May 197

THE BRITISH JOURNAL OF RADIOLOGY

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and related disciplines

The British Journal of Radiology

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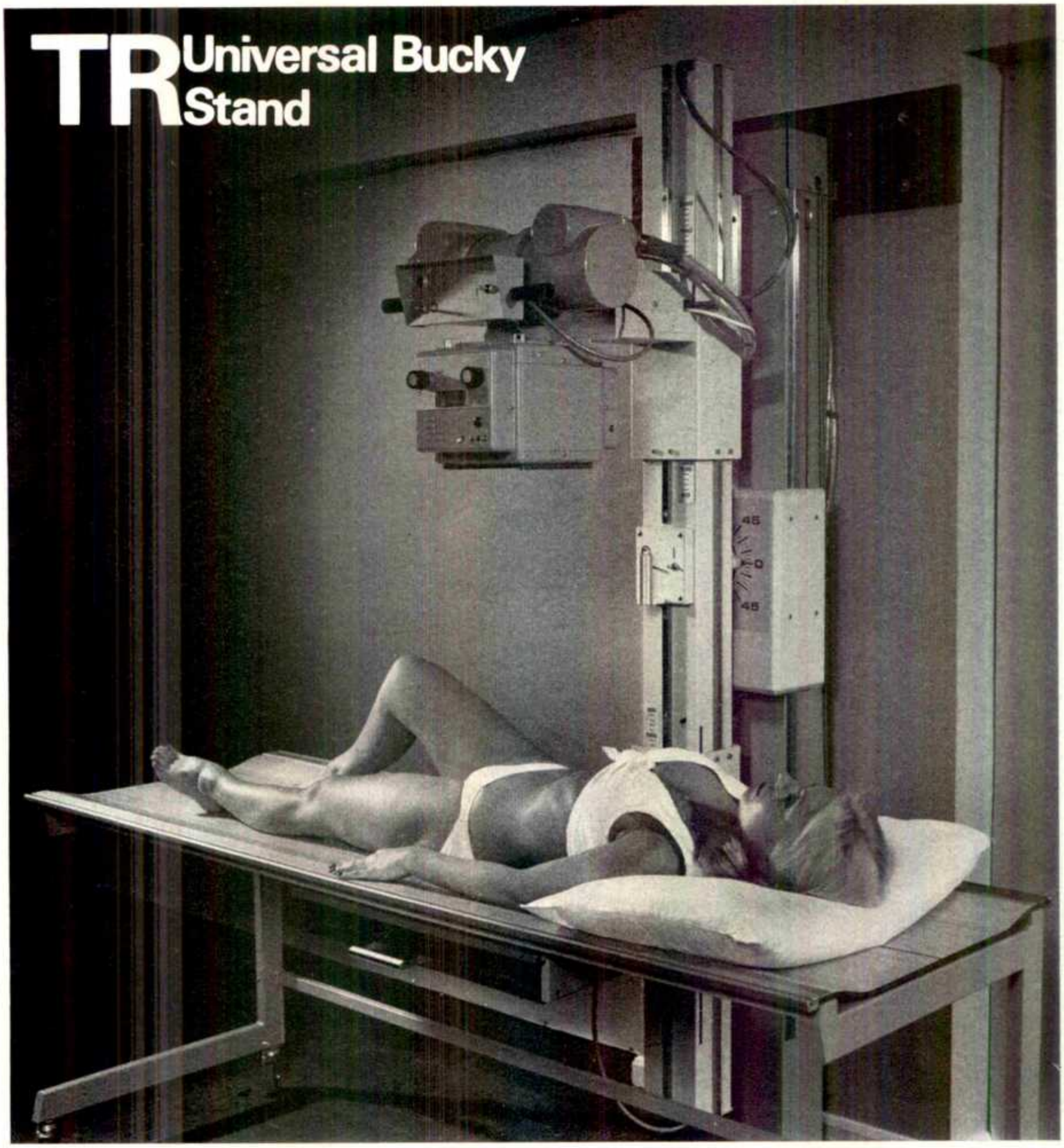

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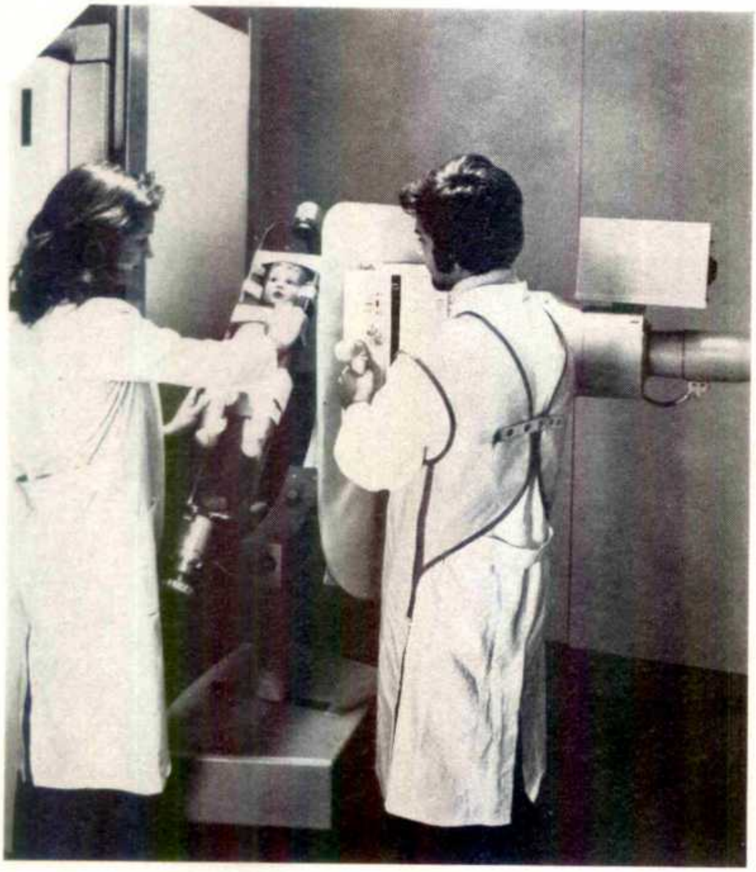

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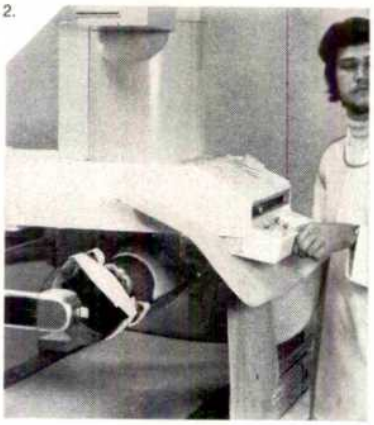

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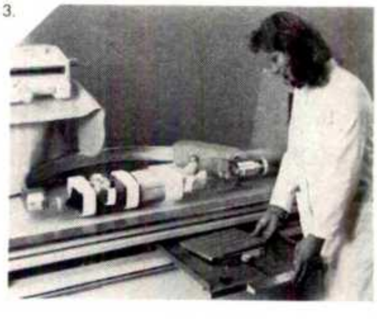

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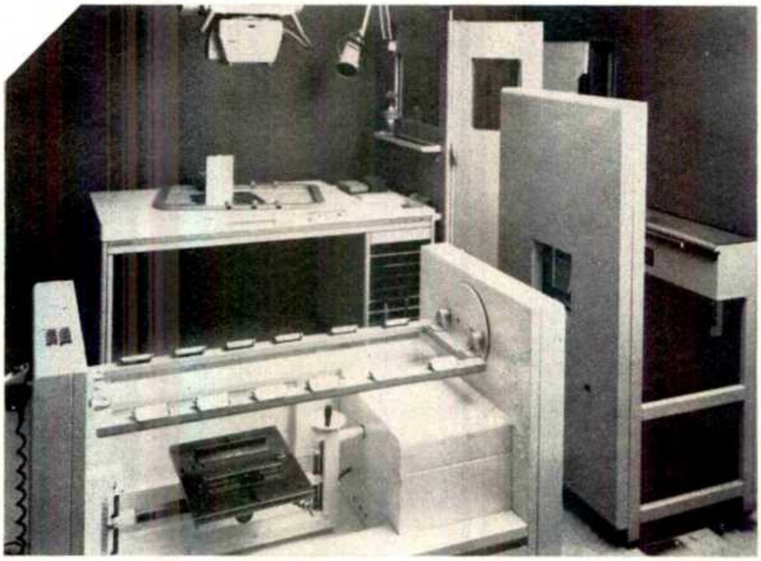
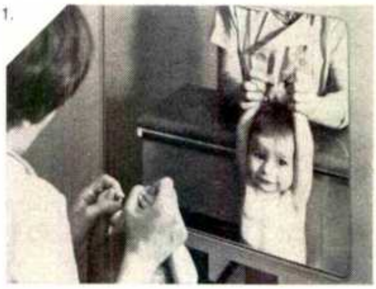


....and met to the full at Karolinska Sjukhuset.

Delegates at the 13th Meeting of the European Society of Pediatric Radiology are cordially invited by the Children's X-ray Department. There you will have the opportunity to see both systems operating under practical conditions. They have been installed for some time now and the personnel have become experienced in their use. You will find a visit both rewarding and revealing.

1.



1. Thorax studies are easily made with the Junior DIAGNOST V. A footswitch enables the exposure to be triggered exactly at the correct respiratory phase. The collimator has been designed to ensure that stray radiation reaching the hands of the radiographer is kept to the safe minimum.

2.

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2. In the case of the Junior DIAGNOST H, positioning is simplicity itself - the tray is moved and not the child. The extremely short object-film distance of approx. 9 mm results in excellent image quality.

3. Tomography with the Junior DIAGNOST T can be performed with the stand horizontal, vertical or in any intermediate position. The tomographic effect is produced by a combined movement of patient support and film cassette with the X-ray tube remaining stationary. The very short time required to complete the blurring movement viz. 0.01 sec. per 4 degrees of arc solves the problem of immobilisation.

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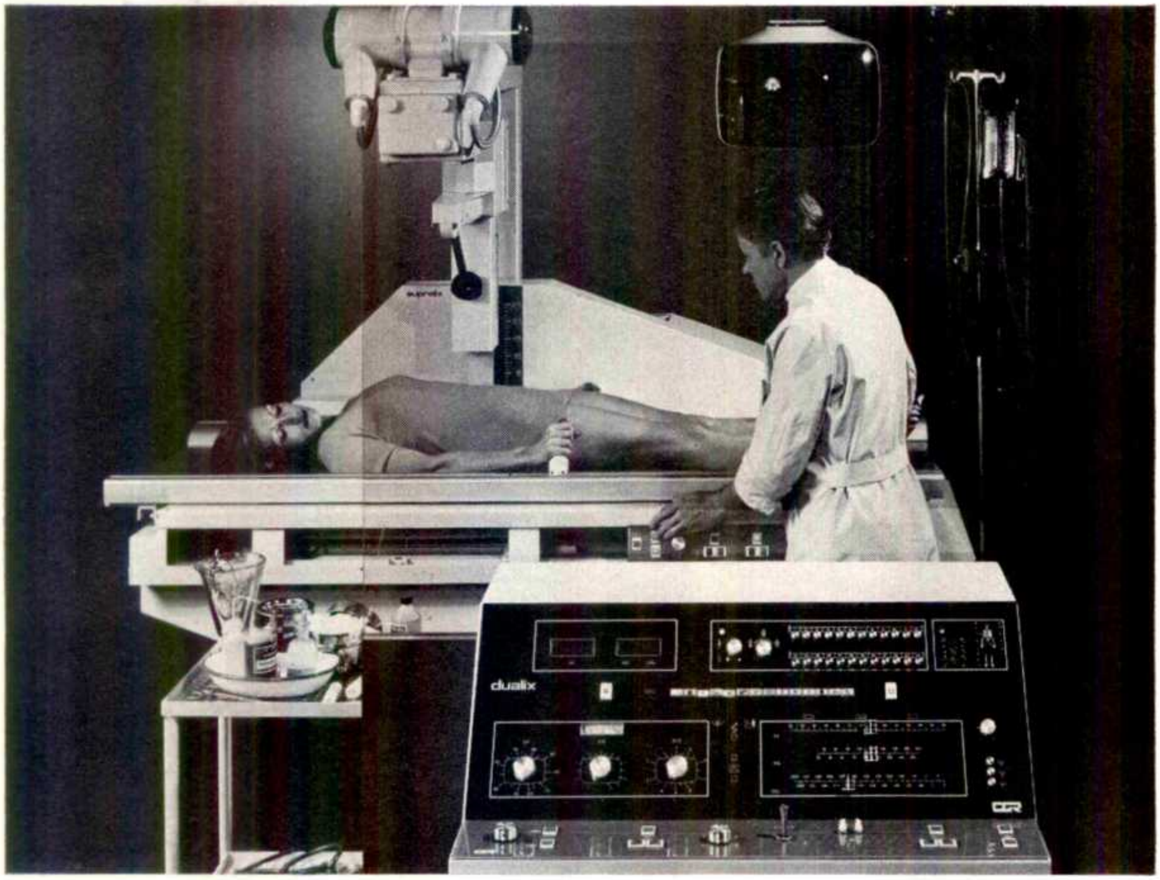

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This complete system has been designed for easy installation and servicing as well as for low running costs.

*The Supradualix is *complete* for less than the cost of many a generator, intensifier and tube alone.

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Mammography: An important announcement from Kodak

New advances in phosphor and emulsion technology have enabled Kodak to announce the 'Min-R' screen and film.

The KODAK 'Min-R' screen and film combination is significantly faster than any mammographic recording products previously offered by Kodak.

The patient receives considerably less radiation. The image is very sharp indeed.

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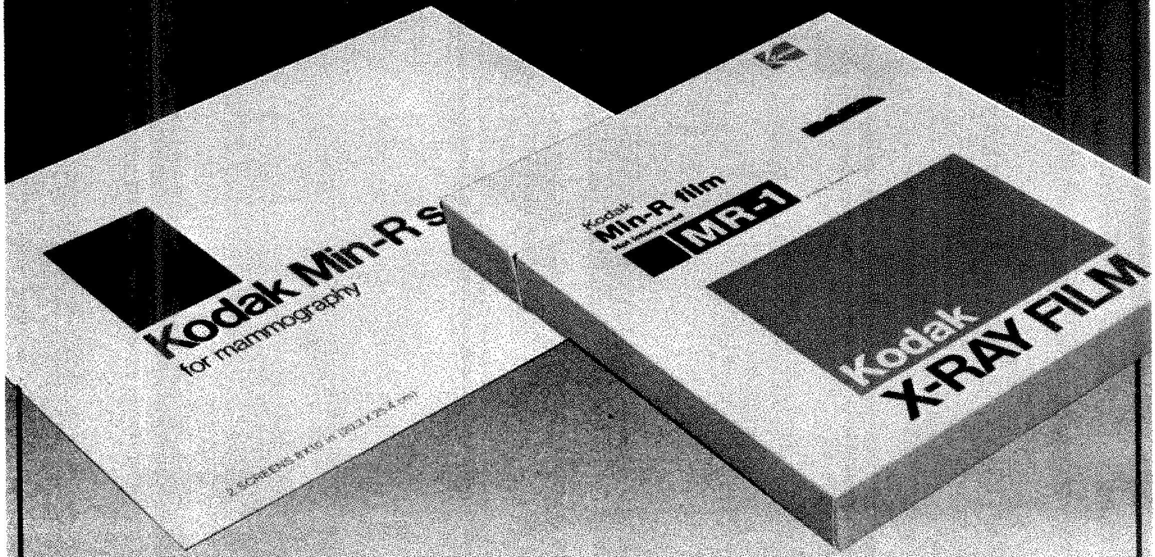

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screen and film for reduced exposure mammography

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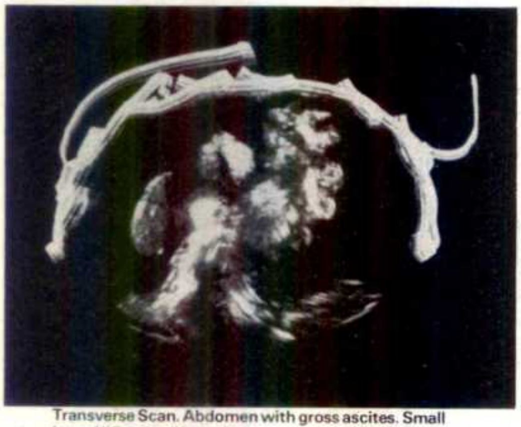
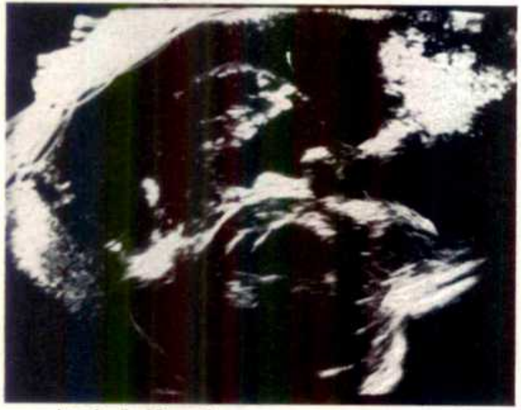
Single Patient Greyscale Study
With the Diasonograph.

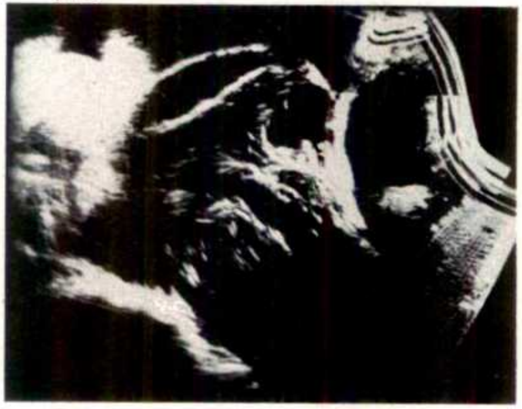


Transverse Scan. Abdomen with gross ascites. Small bowel "floating" in ascites.

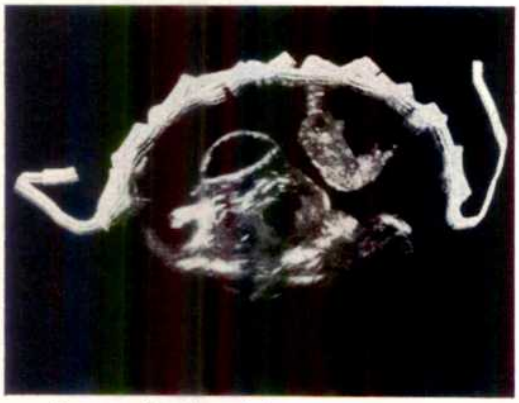
Longitudinal Scan. Multicystic/solid mass arising out of pelvis.



Longitudinal Scan of mass.



Transverse Scan of mass. Ovarian Cystadenocarcinoma.



Transverse Scan. Lower abdomen.

All illustrations courtesy Northwick Park Hospital, Harrow-on-the-Hill.

Full details of the NE 4104G Greyscale Storage Display, NE 4104C Colour Storage Display and of the latest developments in the Diasonograph Ultrasonic Scanner Range on request.

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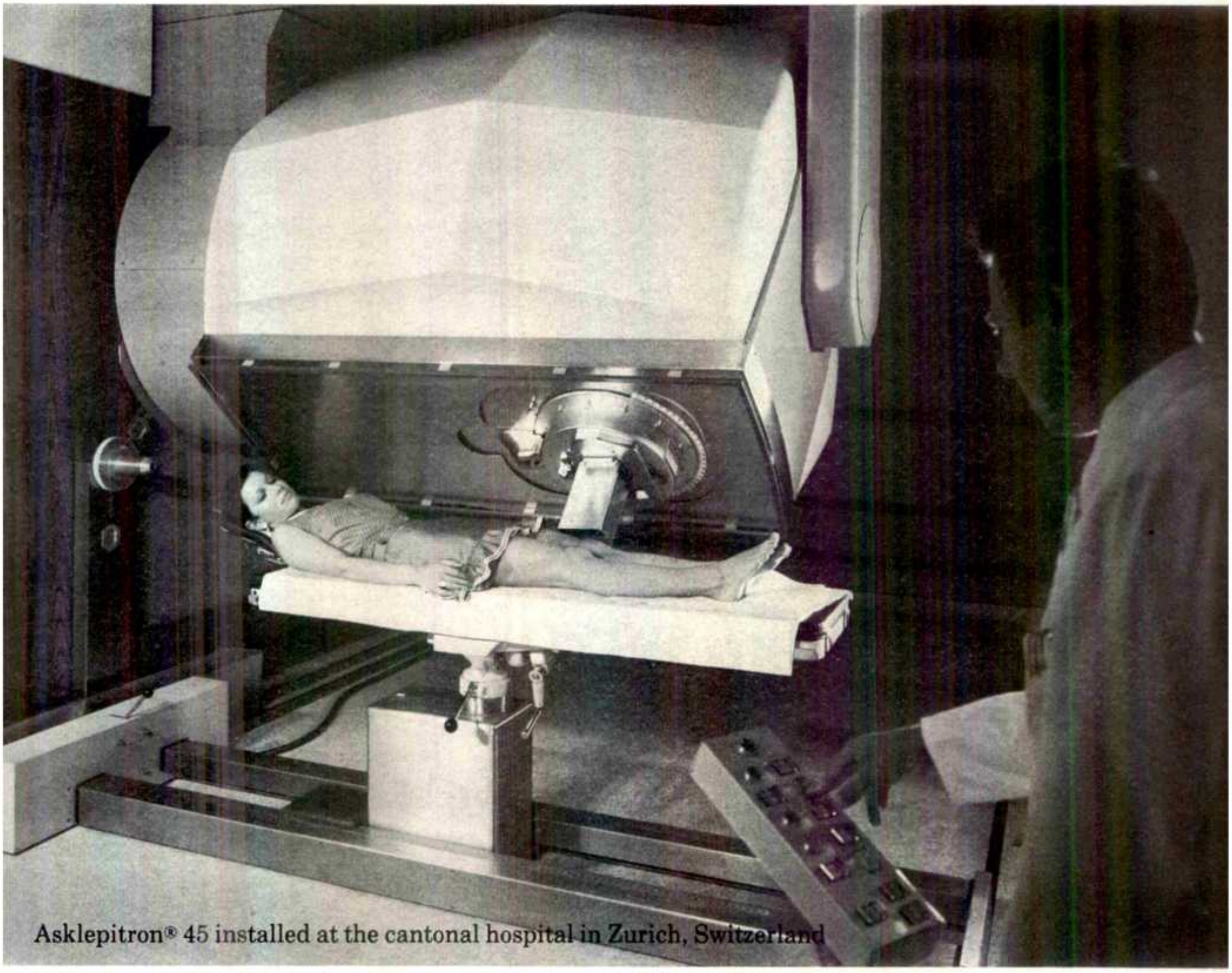

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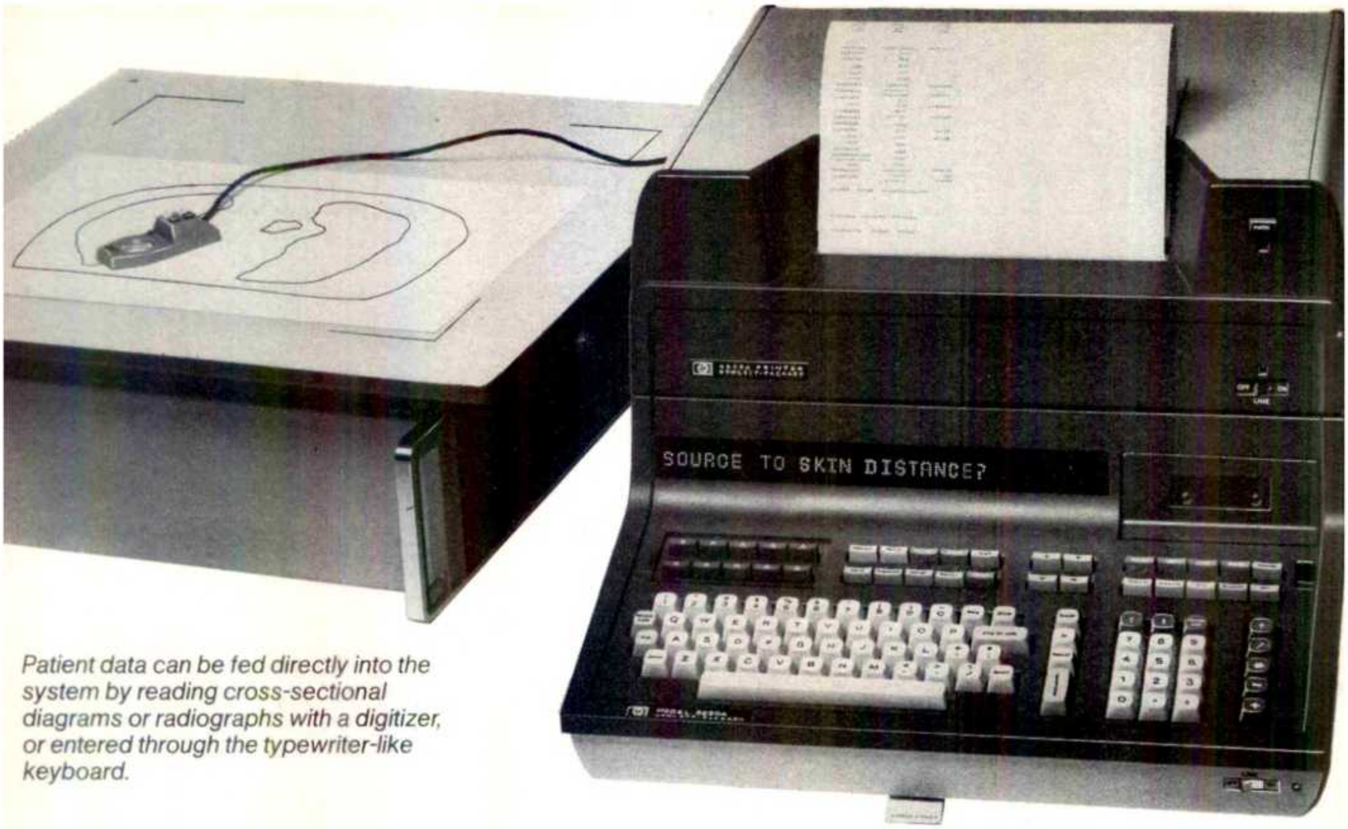

Patient data can be fed directly into the system by reading cross-sectional diagrams or radiographs with a digitizer, or entered through the typewriter-like keyboard.

A series of programs enables the system to produce automatically highly accurate treatment plans for both tele-therapy and brachy-therapy. Computational mistakes and incorrect table readings are virtually eliminated. Therapists have more time for treating patients.

Hewlett-Packard 9830 radiation therapy treatment planning system.

Accurate: fast: graphic: low-cost.

If you are still carrying out radiation therapy treatment calculations by hand, this Hewlett-Packard system will interest you. It carries out this demanding work to a high level of accuracy, in a fraction of the time required to achieve the same results by hand and for far less than you might expect a fully automated system to cost.

The system comes complete with nineteen programs, thoroughly-proven and in regular hospital use. Included are programs covering dose calculations for cesium, radium, cobalt and high-energy electron therapies; treatment calculations for intracavitary, interstitial, regular and irregular fields, multiple and moving beam therapies can be carried out. A general 'book-keeping' dose summary program automatically keeps patient dosage records up-to-date.

The Hewlett-Packard 9830 system is so easy to use that radiation therapy technicians with virtually no previous computer experience can input data and activate the calculating process themselves. Less time spent on doing and checking calculations means more for actual therapy, shorter lead times before therapy can begin, a greater through-put of patients and, possibly, the opportunity to undertake more complex types of treatment.

Moreover, the system is highly flexible. If it is not fully-employed on radio therapy, it can be used to solve problems in many other areas; RIA, medical statistics and so on.

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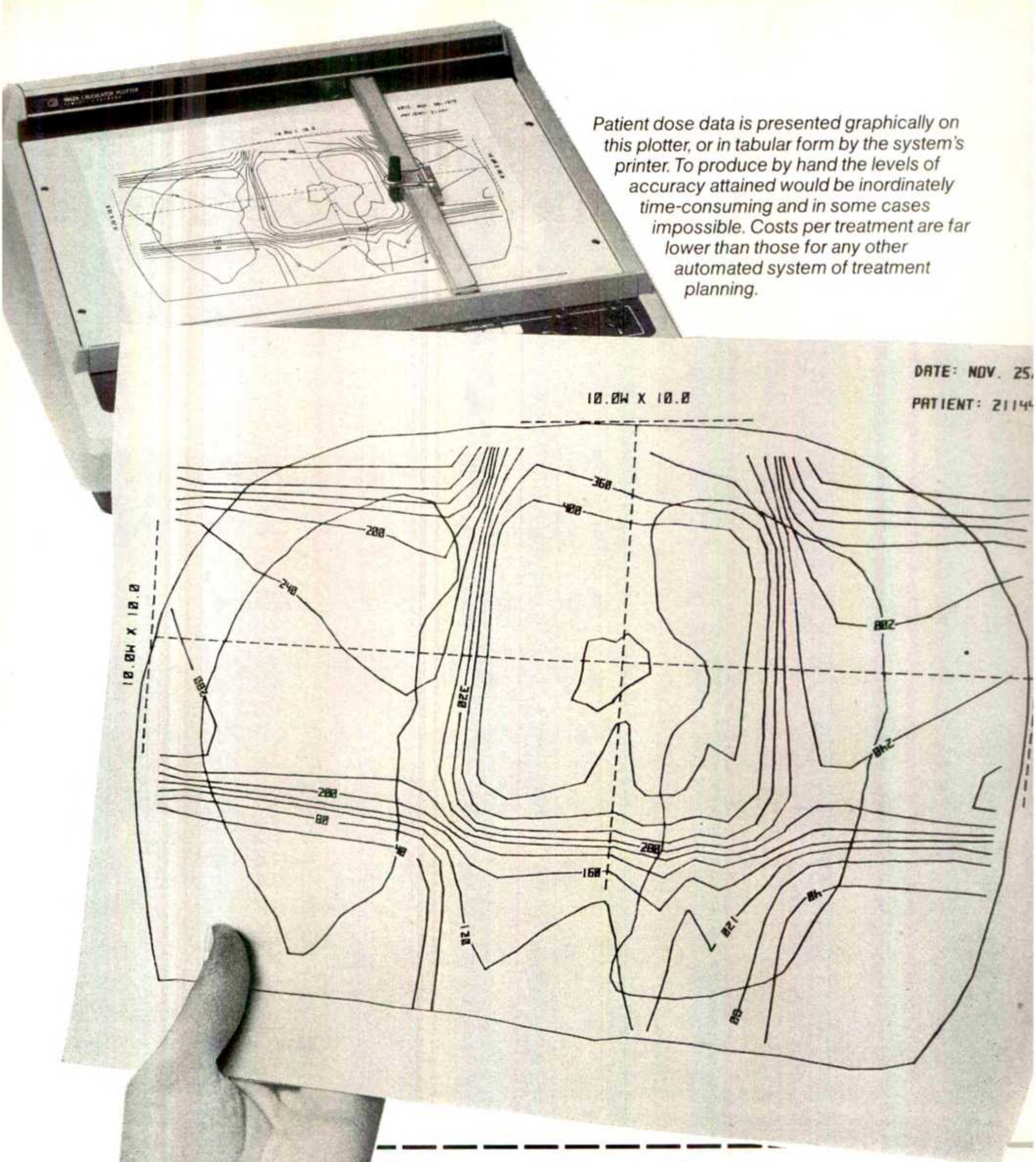

Patient dose data is presented graphically on this plotter, or in tabular form by the system's printer. To produce by hand the levels of accuracy attained would be inordinately time-consuming and in some cases impossible. Costs per treatment are far lower than those for any other automated system of treatment planning.

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complete fact file of the HP 9830 Radiation Thera
treatment planning system. (RAD 3)

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At last, a 5MV linear accelerator that's good enough for the Philips integrated therapy programme.

The Philips Integrated Therapy Programme ensures increased efficiency in the modern radiotherapy department by having a common design philosophy, similarity of operational procedures and simplified service.

The programme embodies maximum reliability and patient safety. It incorporates a long-term plan providing the clinic and hospital with the essential equipment for today and the future.

The new Philips 5MV linear accelerator is the latest introduction to the Programme.

A machine that has been specifically designed for the radiotherapy department needing a unit for X-ray treatments when electron therapy is not required.

Fulfilling an important role.

For the smaller clinic, the SL.75/5 offers all the sophistication of the higher energy linear accelerators in the same series, but it has also been carefully designed to match other units in the 4–6MV range.

For departments where the higher energy machines are already in operation, the common design philosophy of the 5MV enables it to be readily integrated into the department.

All this makes the 5MV ideal as a primary treatment unit or a secondary unit for the larger overworked clinic.

This is what you can expect in performance.

The SL.75/5 will handle 60 patients a day.

The X-ray energy can be set in the 4–6MV range and is monitored and controlled by the same system that is used in the other Philips linear accelerators and so ensures accurate energy stability.

Dose rates at 350 rads per minute at one metre can be achieved at 5MV. (Equivalent to 550 rads per minute at 80cm.)

The maximum field size is 40x40cm at one metre F.S.D.

A 420° gantry rotation has been included to ensure rapid setting up of patient treatments.

All movements are motorised with variable speed control and have simultaneous movement capabilities.

There is also a choice of treatment tables. Either a high lift ram type or an above floor version. (A combination of table side supports and centre spine construction allows beam access from any angle.)

Safety as always.

A major aspect of the SL.75/5 design concerned safety.

The dual channel dosimetry system is backed by a timer. Select and confirm routines ensure maximum patient safety and reduce operational errors. And if required, a verification system can also be added.

Where room protection is limited, a retractable beam absorber is available that can be interlocked to prevent irradiation to unsafe directions.

Dose and time LED displays are automatically maintained in the event of an electrical supply failure.

Find out more about the 5MV and the entire Philips Integrated Therapy Programme.

Here we have made a brief mention of just a few aspects that make the SL.75/5 an important addition to the Philips Integrated Therapy Programme.

The entire Programme includes cobalt units, localiser/simulator, a treatment planning system and ortho-voltage therapy units.

Philips are constantly developing new equipment for the highly specialised radiotherapy field.

If you would like to know more about the Philips Integrated Therapy Programme,
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or The M.E.L. Equipment Company Ltd., P.A.D. Manor Royal, Crawley, Sussex, England,
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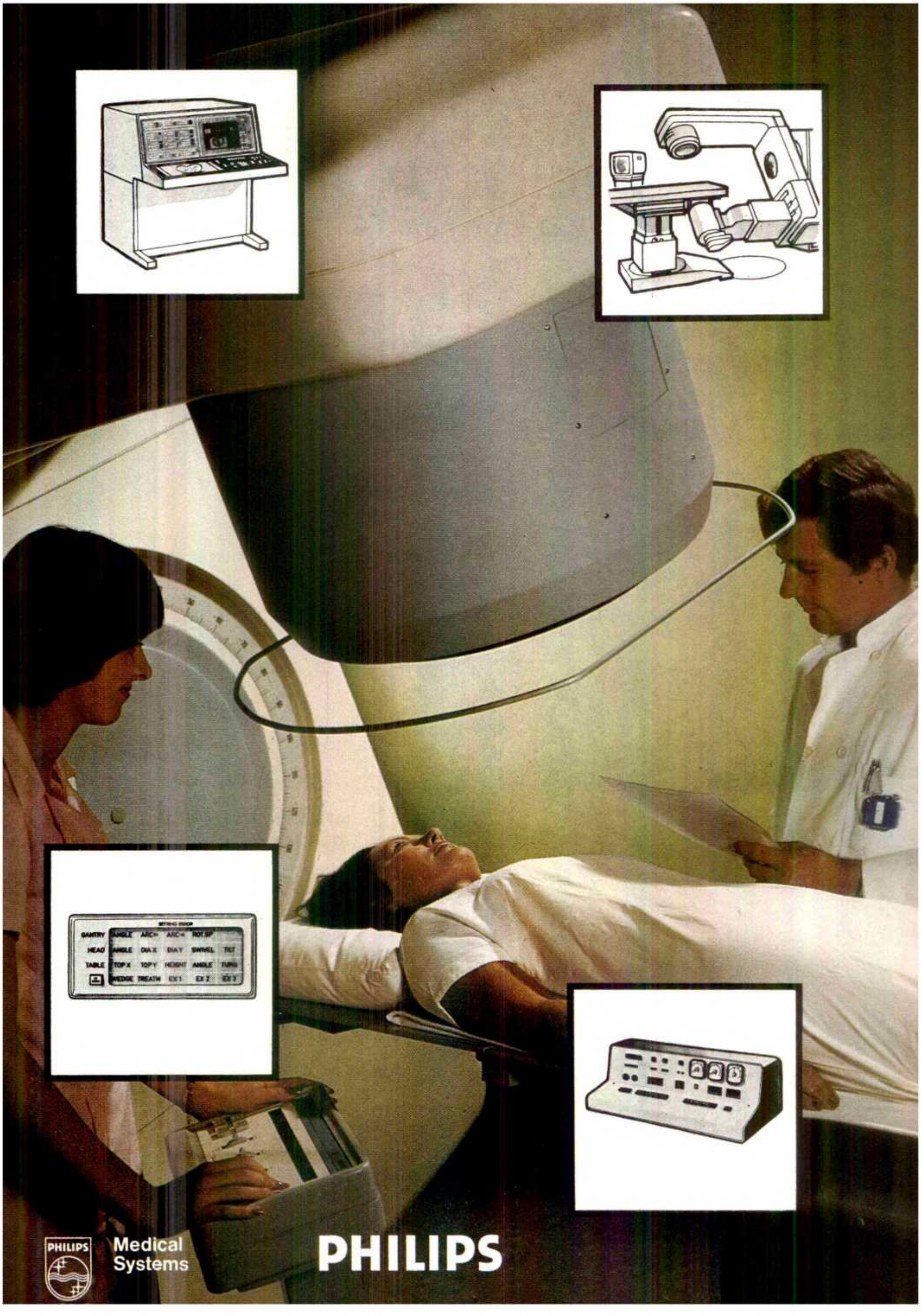
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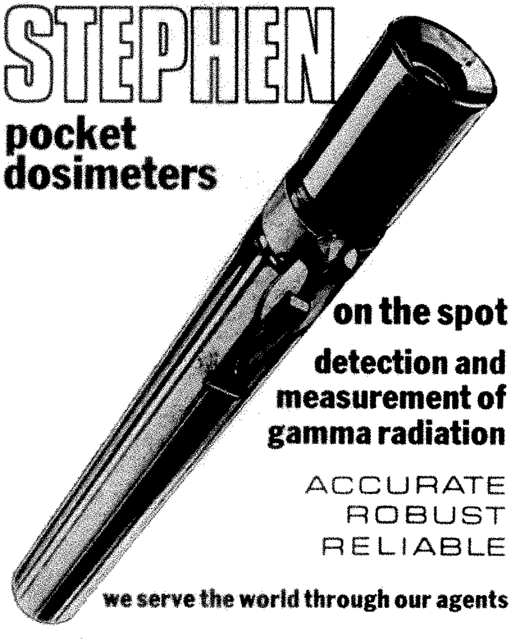

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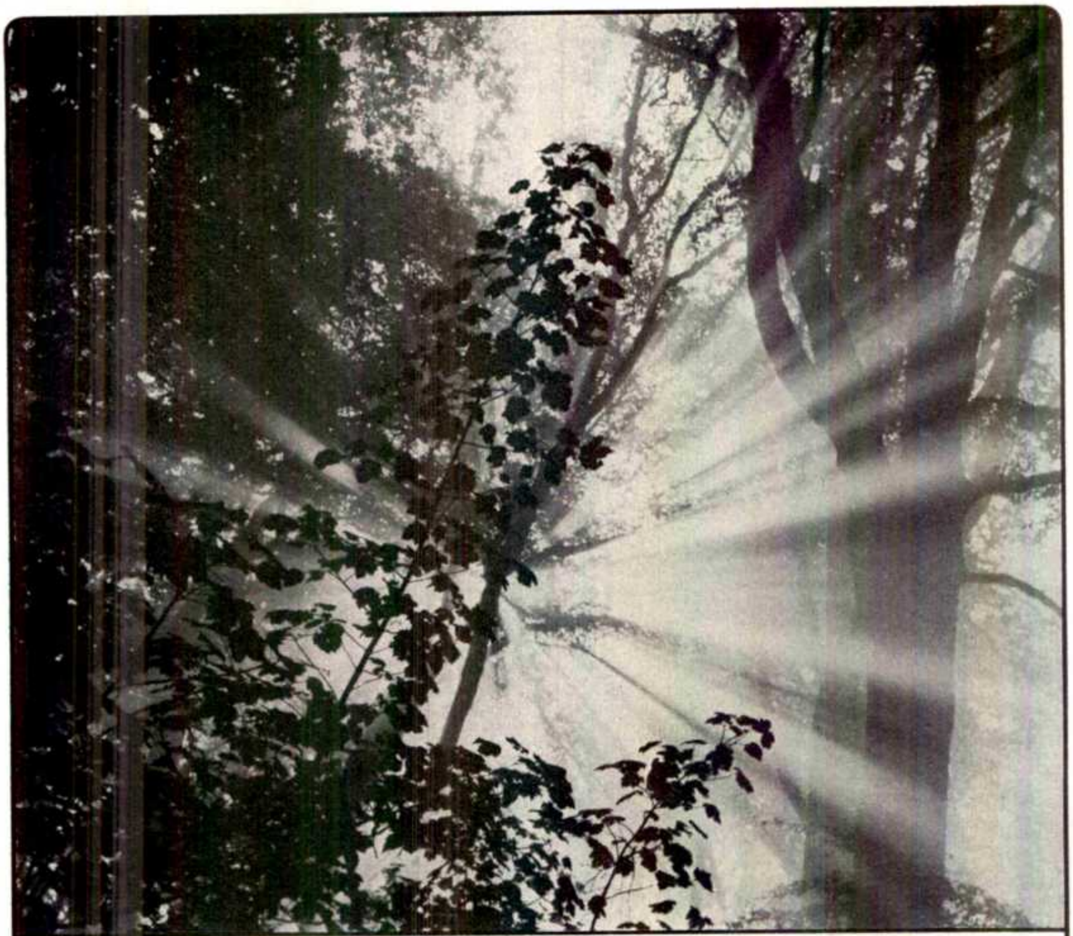
Applications including curriculum vitae, references (publications) should be sent to the director of Swiss Institute for Nuclear Research, Professor Dr. J. P. Blaser, CH-5234 Villigen, not later than 30 June 1976.



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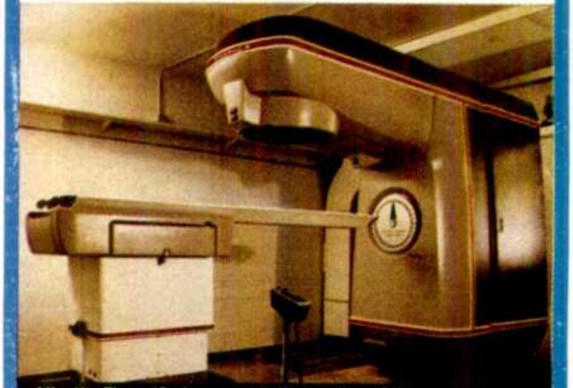
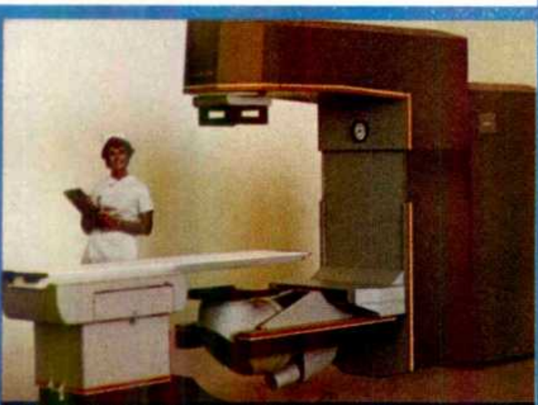


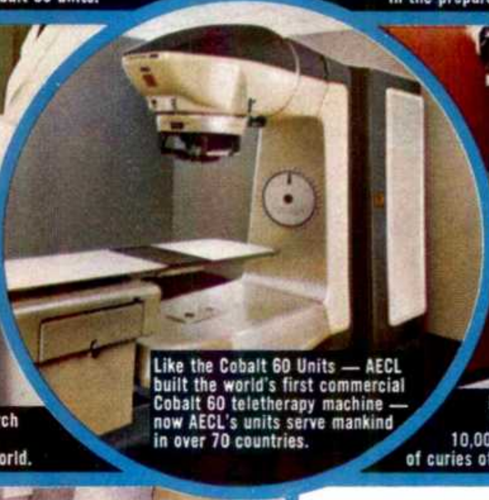
Like the Therac Series — a totally new line of linear accelerators with energy output from 6 to 40 MeV.



Like the Therasim 750 Universal Simulator — AECL pioneered the design of therapy simulators for use with all makes of accelerators, betatrons and Cobalt 60 units.

Like the T.P. 11 treatment planning system — a sophisticated blend of computerization and electronics which adds a new dimension in the preparation of reliable therapy treatment planning.

Like the Gammacell 40 Biological Research Irradiator — Hundreds of AECL research irradiators are in daily use around the world.



Like the Cobalt 60 Units — AECL built the world's first commercial Cobalt 60 teletherapy machine — now AECL's units serve mankind in over 70 countries.

Like medical isotopes — AECL has provided thousands of cobalt therapy sources, nearly 10,000,000 curies of medical cobalt and millions of curies of isotopes for diagnostic and treatment use.

Like the JS 6500 — one of a series of AECL's production line gamma sterilizers for medical disposables in operation on all continents.

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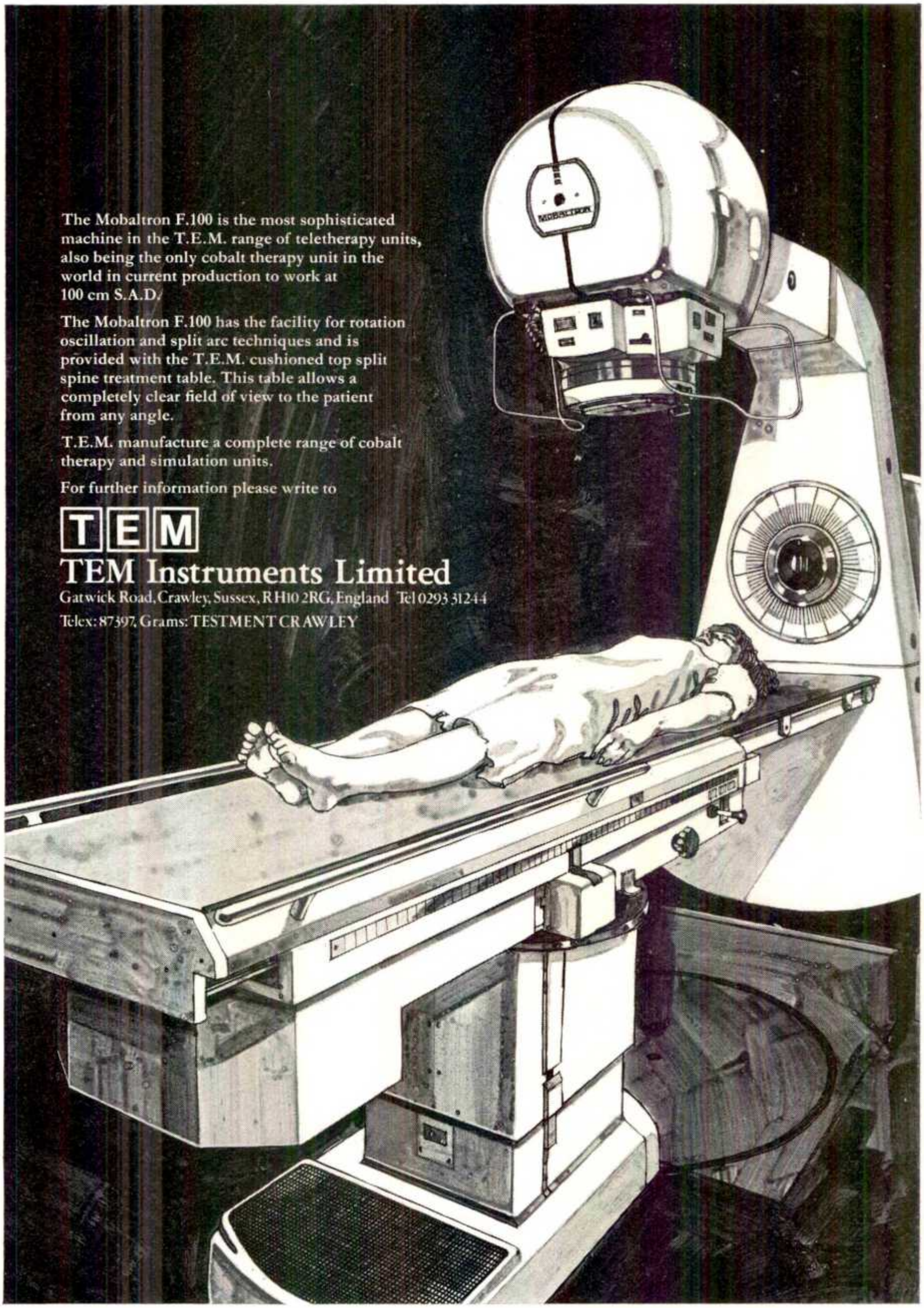

The Mobaltron F.100 is the most sophisticated machine in the T.E.M. range of teletherapy units, also being the only cobalt therapy unit in the world in current production to work at 100 cm S.A.D.

The Mobaltron F.100 has the facility for rotation oscillation and split arc techniques and is provided with the T.E.M. cushioned top split spine treatment table. This table allows a completely clear field of view to the patient from any angle.

T.E.M. manufacture a complete range of cobalt therapy and simulation units.

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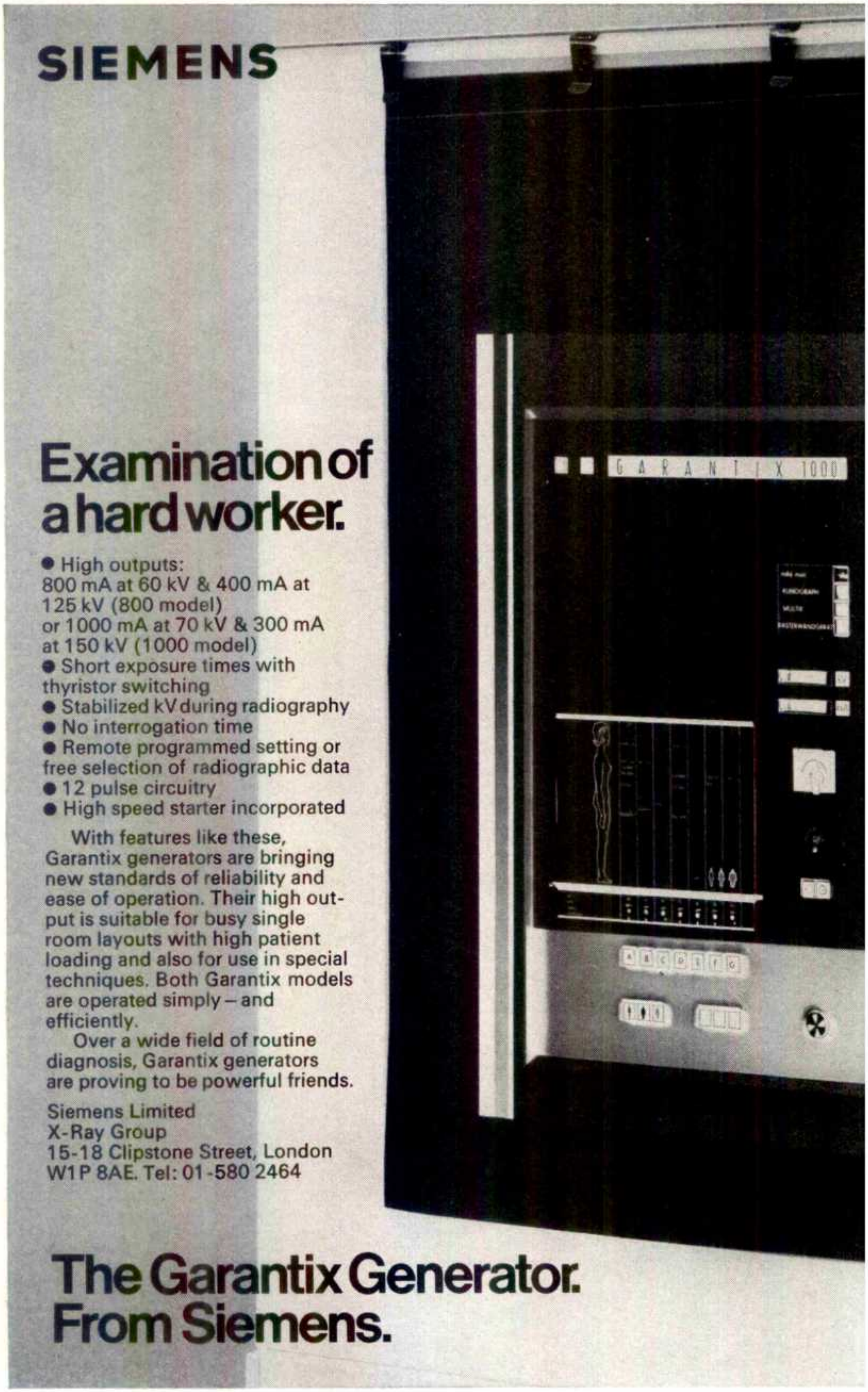

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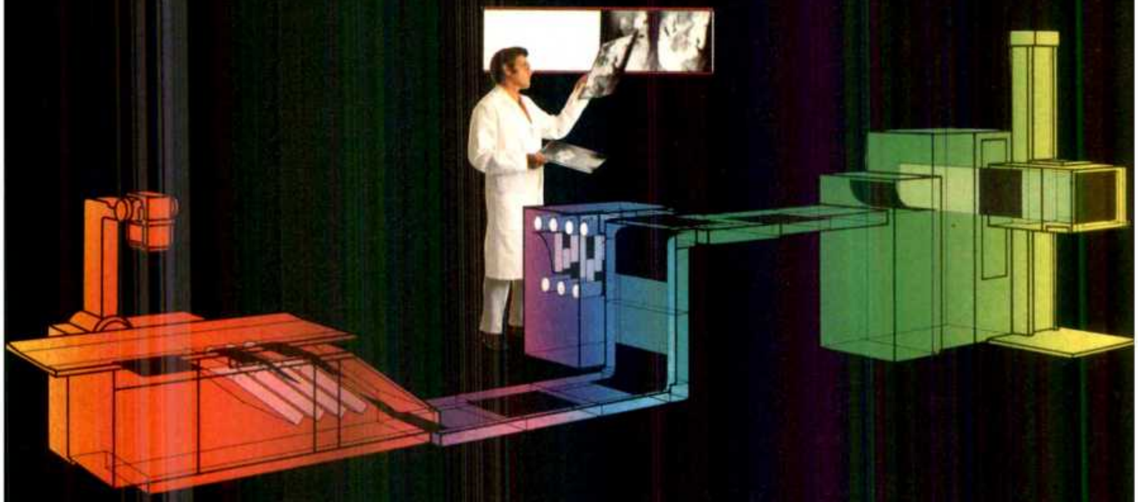

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Full details from Mr. A. J. M. Spaapen, Picker International Operations GmbH, 6201 Auringen- Wiesbaden, Feldberg Strasse 6, West Germany.

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Director of Diagnostic Radiology

Applications are invited from specialist radiologists for appointment to the position of Director of Diagnostic Radiology, The North Brisbane Hospitals Board.

The North Brisbane Hospitals Board controls the Royal Brisbane, Royal Women's and Royal Children's Hospitals and these are major teaching hospitals for the University of Queensland. The Royal Brisbane Hospital provides medical, surgical, out-patient, gynaecological, radiotherapy, casualty, orthopaedic and psychiatric services, with approximately 1,050 beds; the Royal Children's Hospital paediatric treatment with approximately 200 beds and the Royal Women's Hospital obstetric and neo-natal care with approximately 350 beds. The day-to-day running of the complex is in the hands of a Hospital Executive comprising three Executive Directors–Medical Services, Nursing Services and Administrative and Support Services.

Each hospital in turn has a Management Committee comprising the three Branch Heads within that hospital responsible to the Hospital Executive administratively, with each Branch Head having functional responsibility to the appropriate Executive Director.

The Director of Diagnostic Radiology will be responsible to the Executive Director, Medical Services for the radiological services of the Board's Hospitals as a whole and to the Medical Superintendents of the individual hospitals for radiological services within those hospitals.

The University of Queensland has indicated that it will give sympathetic consideration to a request that the Director of Radiology be given formal honorary status in a University Department. The appointment will be permanent after a twelve month probationary period, in accordance with the terms of appointment.

The appointee will be entitled to five weeks annual leave, sick leave, conference leave, and overseas study leave (usually taken at the end of seven years) but by special arrangement with the Board after a shorter period.

The position is full time and superannuated. Salary is $31,920 (Australian) per annum.

Further particulars may be obtained from the Executive Director of Medical Services. Applications giving full details of qualifications, age and experience, together with the names and addresses of three referees should be forwarded to the Executive Director Medical Services, the North Brisbane Hospitals Board, Base Hospitals Post Office, Brisbane 4029, Australia, not later than May 31, 1976.

The Executive Director Medical Services will be visiting the United Kingdom from May 22 to July 31, 1976, and an interview may be arranged through the Agent General for Queensland, Queensland House, London (5572).

THE NORTH BRISBANE HOSPITALS BOARD ADMINISTERING
THE ROYAL BRISBANE HOSPITALS GROUP AND ASSOCIATED HOSPITALS

Deputy Director in-charge, Special Procedures

Applications are called for the position of Deputy Director of Radiological services to be particularly in charge of Special Procedures. The appointee will work under the general direction of the Director of Radiological Services Royal Brisbane complex. The Royal Brisbane Hospital provides medical, surgical, out-patients, gynaecological, radiotherapy, casualty, orthopaedic and psychiatric services and has approximately 1,050 beds.

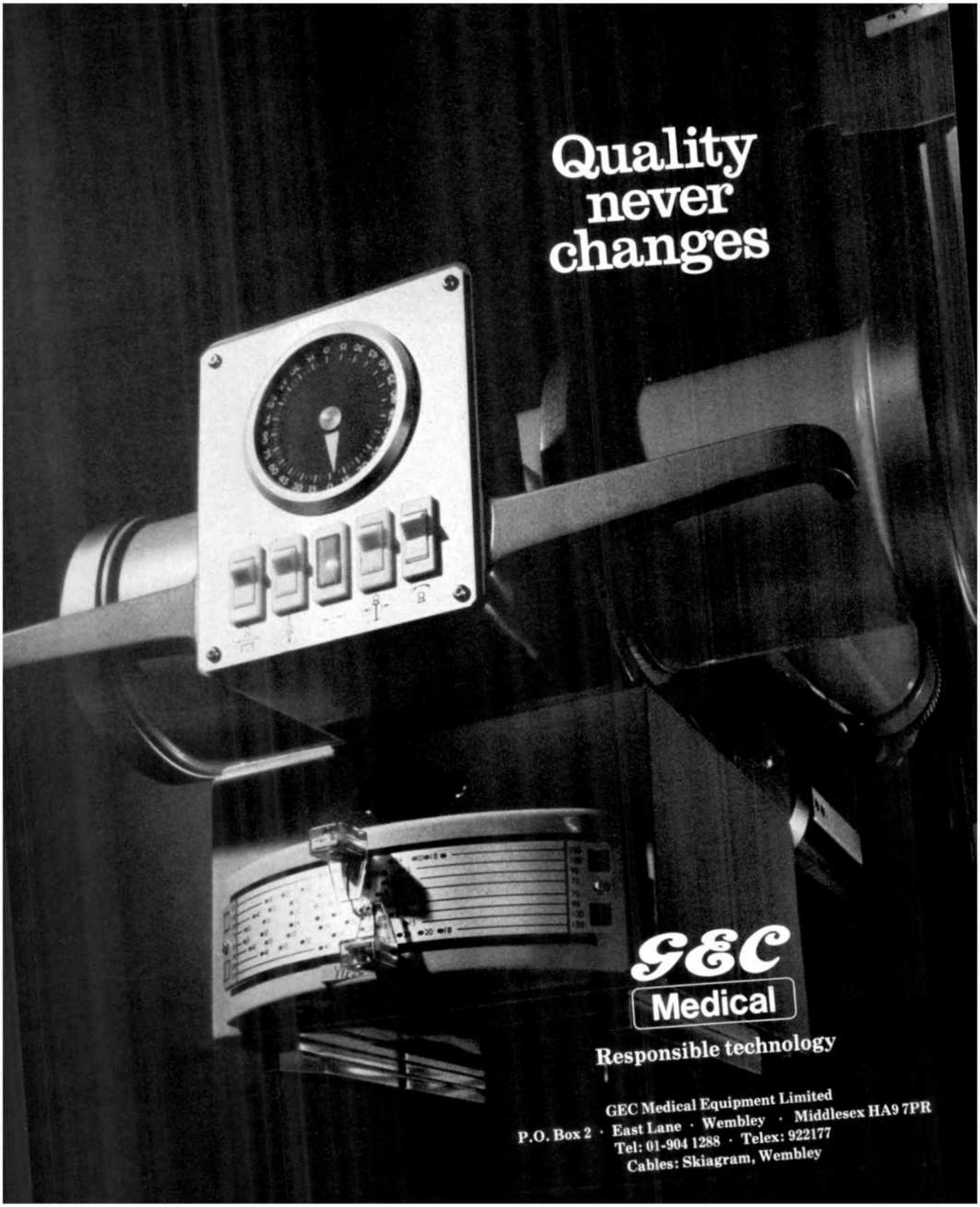
Special procedures would include in the main vascular studies, however, it is envisaged that other organ imaging systems in particular ultrasonics will fall in this category. Plans are being formulated for integration of all organ imaging systems and the appointee would be expected to take an active part in this planning.

The position is full time and carries superannuation, five weeks annual leave, sick leave, conference leave and study leave.

Salary is $29,260 (Australian) per annum.

Further particulars may be obtained from the Executive Director Medical Services and applications, giving full details of qualifications, age and experience, together with the names and addresses of three referees should be forwarded to him at the North Brisbane Hospitals Board, Base Hospitals Post Office, Brisbane 4029 Australia, not later than 31st May, 1976.

The Executive Director Medical Services will be in the United Kingdom from 22.5.76 to 31.7.76 and an interview may be arranged through the Agent-General for Queensland, Queensland House, London (5567).



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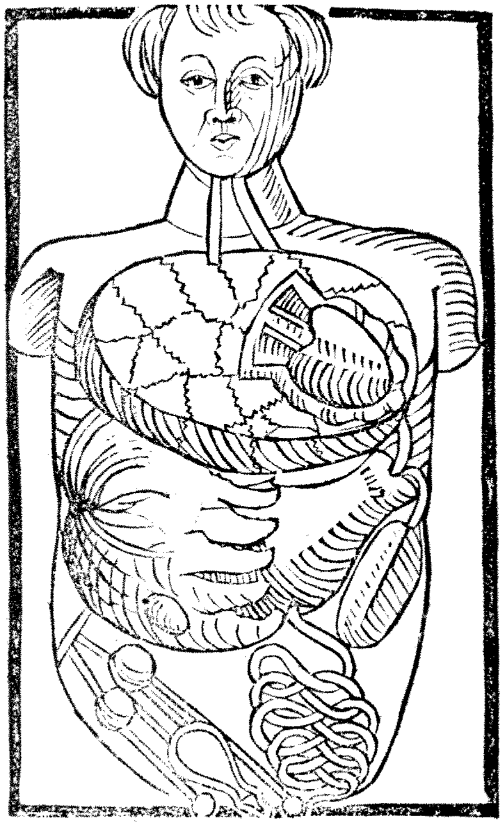

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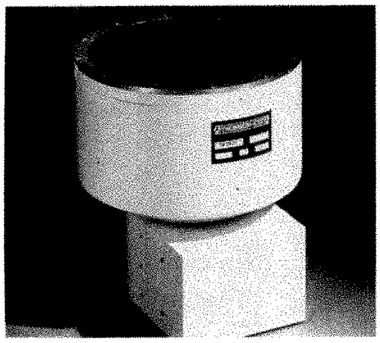

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Applications are called for the position of Deputy Director of Radiology to be in charge of the Radiological Department at the Royal Children's Hospital. The appointee will work under the general direction of the Director of Radiological Services, Royal Brisbane complex. Plans are being formulated for the complete redevelopment of the Radiological Department at the Royal Children's Hospital and the appointee would be expected to take an active part in this planning.

The position would involve an extensive amount of radiological practice in the paediatrics field as well as teaching both under graduate and postgraduate.

The position is a permanent one after a period of twelve months probation.

Five weeks annual leave, sick leave, conference leave and overseas study leave is provided.

Salary is $29,260 (Australian) per annum.

Further particulars may be obtained from the Executive Director Medical Services and applications giving full details of qualifications, age and experience, together with the names and addresses of three referees should be forwarded to him at the North Brisbane Hospitals Board. Base Hospitals Post Office, Brisbane 4029, Australia, not later than 31st May, 1976.

The Executive Director Medical Services will be in the United Kingdom from 22.5.76 to 31.7.76 and an interview may be arranged through the Agent-General for Queensland, Queensland House, London (5577).

Royal Children's Hospital, Melbourne, Victoria, 3052

Applications from appropriately qualified medical practitioners are invited for the position of:

Director of Radiology

The Royal Children's Hospital has at the present time 517 beds. Last year there were 18,926 in-patient admissions and 208, 695 out-patient attendances. The hospital is the paediatric teaching hospital for the University of Melbourne. All aspects of paediatric medicine and surgical care are carried out within the institution.

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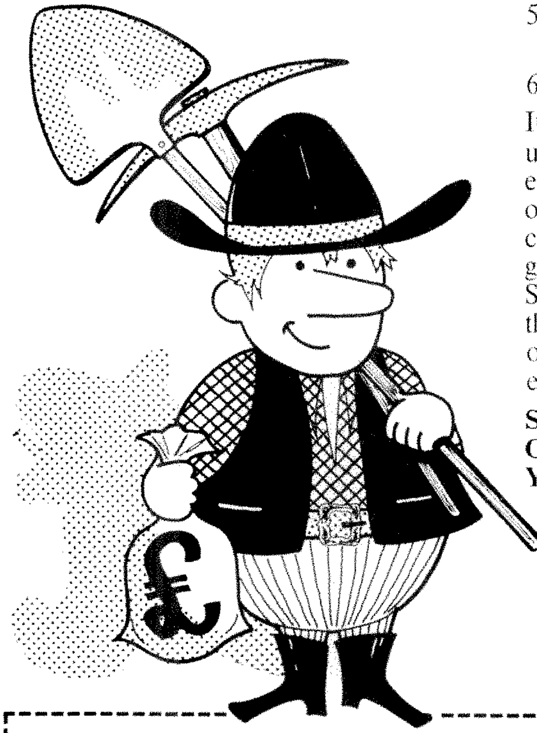

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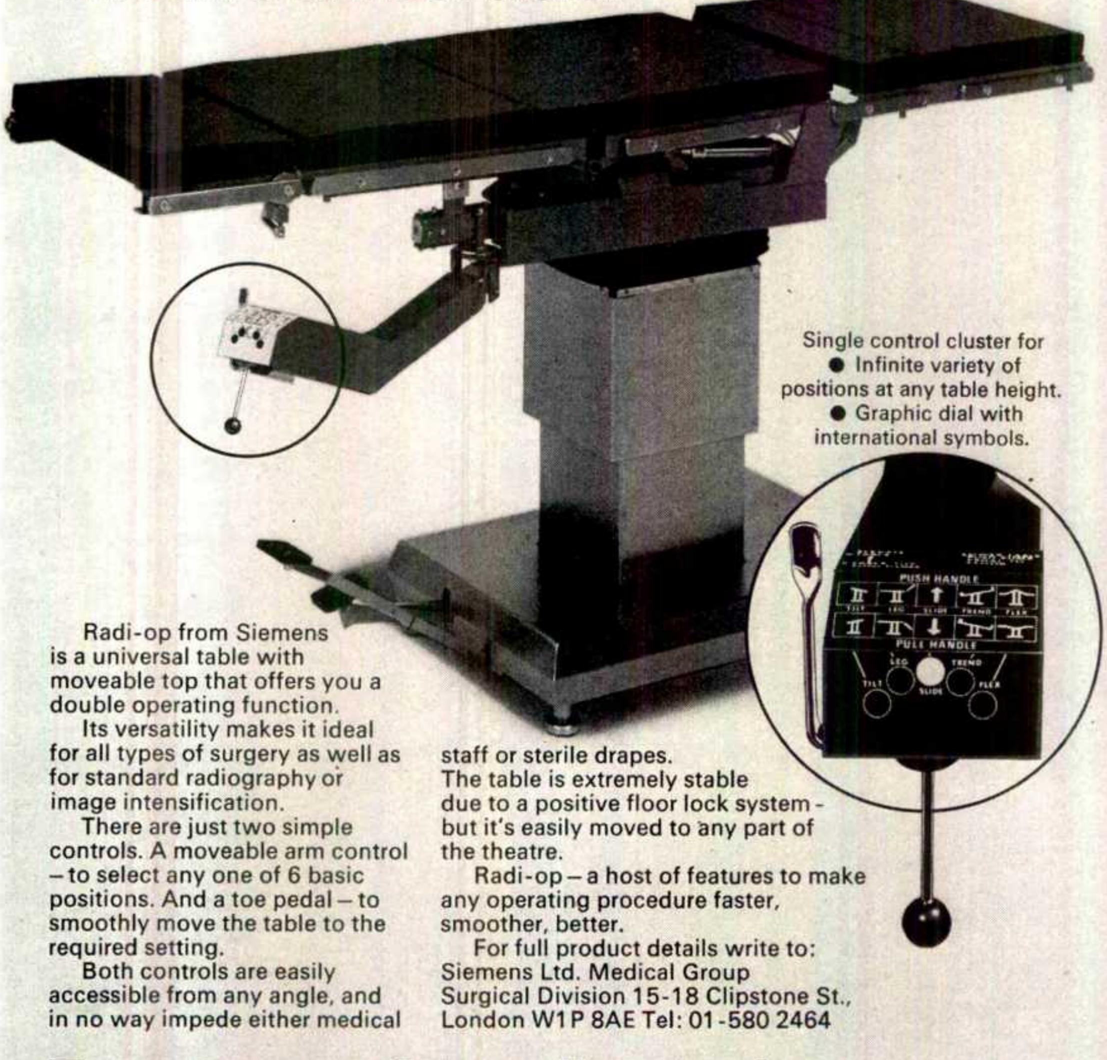

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RADIATION ONCOLOGY OPPORTUNITIES

This new Agency has been established to develop a comprehensive programme in detection, treatment, prevention and education in cancer in this Province of 2·5 million people. A new position of Associate Director of the Agency for Radiation Oncology has been established and applications are being accepted for both this Associate Director and staff.

Full-time salaried staff opportunities exist at the Agency's centres in Vancouver and in Victoria B.C. All positions will be held in conjunction with Faculty positions in the University of British Columbia. Salaries are competitive with those in Canada and the U.S.A. Fringe benefits are comparable to those at the University of British Columbia.

INSTITUTE IN VANCOUVER

Where all the radiotherapy is provided for 2,000,000 of the population in British Columbia and 3,300 new cancer patients are registered per annum. Of these, about 3,000 patients receive radiotherapy for malignant disease. The facilities include the following:

Linear Accelerator	1	280 kV Deep X-ray Unit	1
Cobalt 60 Units	4	Superficial X-ray Unit	1
Caesium Unit	1		

Radium is used for gynaecological cases and for moulds and implants. Other isotopes are also used in treatment.

Pre-clinical work in Radiation Biology is going on now for the "TRIUMF" Cyclotron at the University of British Columbia, with a view to starting clinical trials with negative pi-mesons in about two years. The cyclotron is already working with a beam of low intensity and pi-mesons are being delivered to the treatment room. Basic research in Radiosensitizing agents is also done in the Radiation Biology Section.

The Physics Section in the Institute has four physicists, one assistant physicist, plus technical staff.

An extensive Mould Room and Prosthetics facility is operated in the Institute and this enables a high standard of beam directed radiotherapy to be given, plus the use of moulds, etc. Prosthetics are made for patients coming from all of Western Canada.

There are 56 beds in the Institute and additional gynaecology beds in the adjacent Vancouver General Hospital for radium insertions. Expansion to 85 beds is in the planning stage.

There is an active training programme in Clinical Radiation Oncology and a training programme in Medical Oncology was started in July 1976.

An active Medical Oncology Section is operated in the Institute, and this is being expanded to include work in Clinical Pharmacology. Clinical cooperative therapy trials are also encouraged, including collaboration in national Canadian protocols, and collaboration in U.S.A. protocols.

VICTORIA CLINIC

The Agency's clinic on Vancouver Island is located in the Royal Jubilee Hospital, one of the larger general hospitals in Victoria. This clinic services the largest portion of cancer patients on this island of 400,000 persons.

Between 600 and 700 new cancer patients are seen each year. The equipment includes:

Cobalt 60 Unit	1	Superficial X-ray Unit	1
300 kV X-ray Unit	1		

Radium for Gynaecology cases.

Additional equipment is being planned for installation over the next two years, along with a mould room. The physicist at present works half-time in the clinic and half-time at the University of Victoria (Physics Department); a full-time physicist member of the Agency's Physics Section is planned.

At present there is one Radiation Oncologist on the Victoria staff and this is now being increased to two. Two new Medical Oncology positions have also been established. Preparations for integration of all Victoria Clinic activities with those of the Institute are under way, to include a training programme.

Applicants should apply, stating areas of special interest within Radiotherapy (e.g. Paediatrics, Gynaecology, etc.) to Thomas C. Hall, M.D., Director, Cancer Control Agency of British Columbia, 2656 Heather Street, Vancouver B.C., Canada, V5Z 3J3, and include a curriculum vitae, time of availability, and expected salary range.

SPECIAL SUMMER PROGRAMS AT M.I.T.

PRINCIPLES OF NUCLEAR MEDICINE 12–16 July 1976

This Program will deal with the state of the art in nuclear medicine with emphasis on physical aspects. Topics to be covered include instrumentation, radiopharmaceuticals, dosimetry, and data processing as well as specific organ studies and therapy.

PRINCIPLES OF COMPUTERIZED AXIAL TOMOGRAPHY, 19–23 July 1976

This Program will deal with the state of the art in computerized axial tomography with emphasis on physical aspects. Topics to be covered include the physics of radiation interaction with biological tissues, instrumentation, algorithm development and computer systems for image reconstruction, the use of contrast agents, artifacts—cause and cure, and specialized areas of imaging.

The programs should be of value to both physicians and physical scientists working in the areas. They are jointly sponsored by the Harvard Medical School and M.I.T. through the Harvard–M.I.T. Program in Health Sciences and Technology. For further information write to: Director of Summer Session, Room E19–356, M.I.T., Cambridge, Ma. 02139.

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Dr. E. W. Emery: Royal Postgraduate Medical School, Hammersmith Hospital, W.12;
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Interested persons in the United Kingdom should obtain the information sheet relating to this post from the London Representative, University of the Witwatersrand, 278 High Holborn, London, W.C.1. Applications should be lodged with the Registrar, University of the Witwatersrand, Jan Smuts Avenue, Johannesburg, 2001, South Africa not later than June 15, 1976.

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The Department of Radiology, Harvard Medical School is sponsoring a course in Bone and Joint Radiology to be held October 25–27, 1976 at the Hyatt Regency Hotel in Cambridge, Massachusetts.

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Further information can be obtained by writing to:
Associate Dean, Department of Continuing Education,
Harvard Medical School, 25 Shattuck Street, Boston,
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POSTGRADUATE COURSE IN NUCLEAR MEDICINE

The Department of Radiology, Joint Program in Nuclear Medicine of the Harvard Medical School is sponsoring a postgraduate course "Clinical Nuclear Medicine: 1976" to be held September 9-11, 1976, at the Hyatt Regency Hotel in Cambridge, Massachusetts.

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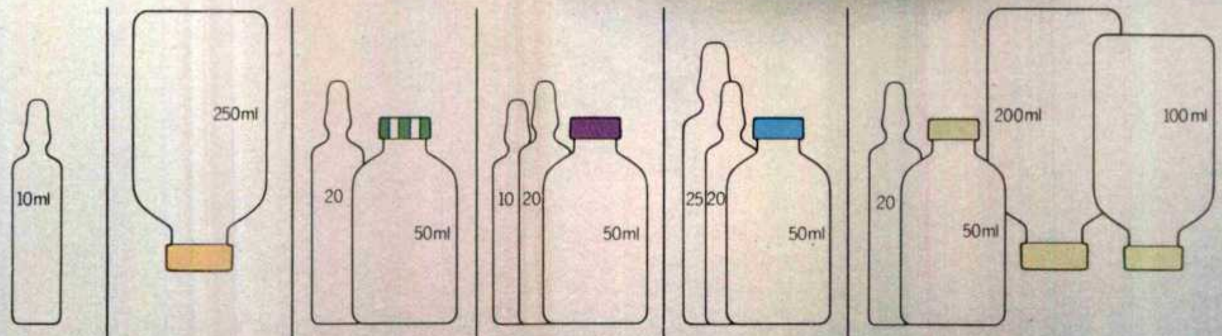

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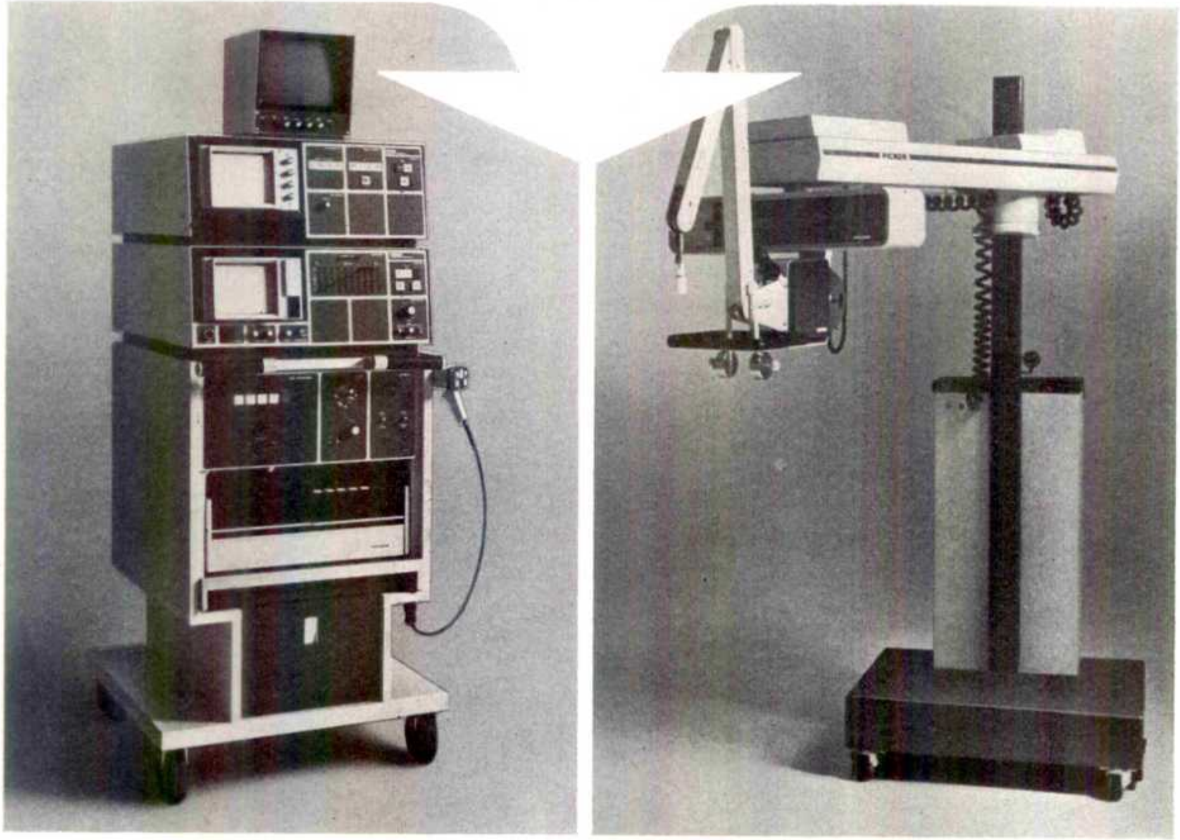

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1976, *British Journal of Radiology*, *49*, 391–392
VOLUME 49 NUMBER 581 MAY 1976

The British Journal of Radiology

Radiology now

SI Units

The International System of Units (SI) was adopted internationally in 1960. In 1968 the Royal Society of Medicine organized a conference of medical editors to discuss the introduction of SI units, but their recommendations did not appear until 1972 (Ellis, 1972). Now another, more comprehensive book on the subject has appeared (Armstrong Lowe, 1975). Nevertheless, few journals have made a complete change to the new system. Why the long delay?

In the medical field no doubt writers have held back until the hospitals had changed over internally to the new system. With the publication of the Health Service Circular H.S.C. (I.S.) 140 in May 1975 the situation is likely to change very shortly. That circular instructed the National Health Service to change to SI by December 1, 1975; there may have been some slipping on the time schedule, but the change will probably have been made throughout the service by the time this annotation appears. In the medical field the principal change seems to be over the units of concentration (of drugs, chemicals, etc.) and of blood gases. In future, expressions such as per cent, ppm are not to be allowed, and concentrations are to be expressed in mmol/litre (mmol/dm^3), or g/litre when the substance has no defined molecular weight. The partial pressure of blood gases is to be given in kilopascal (kPa).

Part of the reason why the introduction of the SI has been so slow is probably because people are not sure how many exceptions to the full rigour of SI will finally be allowed.

In this connection, the R.S.M. booklet remarks "There is a place for special units which are not SI when they are used for a limited range of application connected with medicine. In addition it is felt strongly that measurements should be quoted in the units in which the measurement is made. In medicine, for example, the current international practice of using mmHg for blood, intrauterine and intra-ocular pressures is maintained and for intrathecal pressures cm H_2O. For blood pressure mercury manometers are used in most countries and mmHg is the unit recommended." However, the new W.H.O. book (Armstrong Lowe, 1975), which is extremely comprehensive and includes about 2,000 different quantities, does not mention blood pressure. It states firmly that the pascal is the unit of pressure but that the bar and the normal atmosphere will be accepted for a limited time.

One of the reasons for the choice of the old, non SI units was that they should have a reasonable magnitude. In many specialized fields of study the magnitude of the SI unit is inconveniently big or small. It is of great interest to know which of these fields will succeed in keeping their special units. One successful group is astronomers who have succeeded in retaining the parsec and the astronomical unit (but not the light year). Nuclear and atomic physics is at the other end of the scale. The electron volt and the atomic mass unit are still to be allowed (according to Armstrong Lowe, (1975)) although the symbol for the latter is to be u instead of a m u. The barn, however, is allowed only for the time being; it seems that ultimately a nuclear cross-section of 1 mbarn will become 10^{-31} m^2 or about 300 am^2. The new unit of activity, the becquerel, is another example of inconvenient size (Nicholson, 1976).

One wonders whether the SI, when carried to its logical conclusion, is not a demonstration of the vice of tidy-mindedness. Certainly the continued use of some of the old units seems still to be under review. The new book from W.H.O. (Armstrong Lowe, 1975) does not leave the reader confident that no further changes will be made; the omission of blood-pressure from the 2,000 quantities listed leaves the reader in a state of doubt. The book does, however, have a number of points in its favour. Besides its comprehensive coverage, there are separate alphabetical sections based on the name of the quantity, the name of the unit and the symbol of the unit. There are also conversion factors relating non-SI to SI units and a table of the fundamental physical constants. These features are a great help when consulting the book.

Finally there is the question of the policy of this journal. We cover such a wide variety of disciplines that it would be difficult to insist on a sudden change to SI for all papers, particularly when the future of some of the special units is still in doubt. The SI units for radiology (Gy and Bq) have only recently been agreed (Boag and Binks, 1975; *The Lancet*, 1975) and will certainly not be universally introduced at once. Rather, we must expect a gradual change reflecting the progressive introduction of SI into the National Health Service and the various laboratories which contribute papers to the Journal.

D. K. BEWLEY.

REFERENCES

ARMSTRONG LOWE, D., 1975. A guide to international recommendations on names and symbols for quantities and on units of measurement. World Health Organization, Geneva.

BOAG, J. W., and BINKS, C., 1975. The introduction of S.I. units into the radiological sciences. *British Institute of Radiology Bulletin 2*, 6.

DEPARTMENT OF HEALTH AND SOCIAL SECURITY, 1975. Health Service Circular H.S.C. (I.S.) 140.

ELLIS, G., 1972. Units, symbols and abbreviations. *The Royal Society of Medicine.*

The Lancet, 1975. More on units, especially for radiobiology, *2*, 722.

NICHOLSON, J. P., 1976. New terminology needed. *British Journal of Radiology* (in press).

Book review

Traité de Radiodiagnostic. Tome VII. Foie, voie biliares, Pancreas, Rate. By G. Delorme and J.-P. Monnier, pp. 559, 619 illus., 1975 (Paris, Masson & Cie), F.540.

This book forms a part of the prestigious French handbook of radiodiagnosis, comprising a total of 20 volumes of which seven have already been published.

This volume covers the radiodiagnostic problems related to the liver, bile-ducts, pancreas and spleen. In addition to the radiological aspects, two large sections are devoted respectively to scintigraphy and ultrasound tomography of these organs.

The first part (144 pages) is devoted to the liver. Subjects deal successively with anatomy and physiology, radiological techniques, normal images and finally pathologic conditions. Taking into account the important role of angiography in the diagnosis of liver disease, the detailed and fine descriptions of the angiographic findings should be especially praised.

The second part (100 pages) deals with the bile-ducts and contains a well-balanced and lucid presentation of the anatomic and physiologic base of the study of biliary disease.

In Chapter VI of this part, which is devoted to the different examination techniques of the biliary-ducts, no mention is made of the method of transvenous cholangiography. The reviewer would also have preferred a somewhat more detailed discussion of the contrast media used in cholangiography.

The pancreas is ably discussed in Part 3 (84 pages) and is superbly illustrated, especially the section on pancreatic neoplasms.

In the fourth part (40 pages) the authors deal exclusively with the opacification of the biliary and the pancreatic ducts either by means of endoscopic catheterization of Vater's ampulla or by direct peroperative methods. In the opinion of the reviewer both techniques could as well have been included in the two previous parts dealing respectively with the biliary tracts and pancreas. Indeed several conditions related to both organs and already described in the two previous parts are now discussed again but only in relation to these two techniques.

Part 5 (42 pages), on the spleen, is to be admired for the original and beautiful coverage of the various morphological and topographic forms of the normal spleen.

Part 6 (73 pages) deals again with examination techniques, a large section being devoted to scintigraphy of the liver, pancreas and spleen. In addition to sections dealing with ultrasound tomography and laparoscopy, this part includes also a detailed discussion of two techniques which are relatively little known outside the French literature. The "enlarged carboxy angiogram" permits the visualization by means of a gas (CO_2) of the subhepatic and intrahepatic veins. In the opinion of the reviewer this method can be very useful for the study of abnormalities of the subhepatic veins but is of only minor importance in the study of space-occupying lesions of the liver which can be diagnosed better by arteriography. The second technique concerns hepato- and splenography after either intra-arterial, intraportal, intravenous or intrasplenic injection of liposoluble iodinated contrast media. Although the morphologic information thus obtained in space-occupying lesions of the liver and spleen looks very attractive, most radiologists outside France are reluctant to apply this method because of the risk related to the parenteral administration of lipiodol.

The seventh and last part (32 pages) deals exclusively with the radiologic exploration of syndromes of portal hypertension. This section includes all recent technical developments in this field. The haemodynamic studies and the study of portal hypertension treated by operation should especially be mentioned. One is surprised that so little space is allotted to the discussion of portal hypertension due to prehepatic block.

The text of this book is generally very well done and very clear. The printing is almost flawless. The text and legends are remarkably free of typographical errors. The quality of the carefully-selected radiographic reproductions can simply be rated as superb.

This work compares favourably with the previously published volumes of this handbook, and can be recommended without reservation. It will serve as instruction for trainees in radiology and as a valuable reference for the general radiologist.

A. BAERT.

1976, *British Journal of Radiology*, *49*, 393–397 May 1976

Measurement of regional pulmonary oedema in man using radioactive water ($H_2{}^{15}O$)

By F. Fazio, M.D.,* T. Jones, M.Sc., C. G. C. MacArthur, M.B., M.R.C.P., C. G. Rhodes, M.Sc., R. E. Steiner, M.D., F.R.C.P., F.R.C.R., and J. M. B. Hughes, D.M., M.R.C.P.

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Abstract

Regional extravascular lung water (rELW) has been measured in normal subjects and in patients with left heart diseases using a double-indicator dilution technique and external counting over the chest. Gamma-emitting radioisotopes were injected intravenously, $^{113}In^m$ as a vascular non-diffusible indicator, and $H_2{}^{15}O$ as a freely diffusible indicator. Time activity curves were then recorded over the upper and lower zones of the lung in the supine position with external probes. rELW per unit of blood volume and rELW per unit of blood flow were increased in patients with raised left atrial pressure even in the presence of radiologically clear lung fields. There was a uniform distribution of these ratios between upper and lower zones in normals, whereas in patients rELW was preferentially distributed in the lower zones.

The only established method for assessing the regional distribution of pulmonary oedema is the chest X ray (Kerley, 1962). However, lung fields may be clear in some clinical situations when pulmonary oedema is suspected. When the lung becomes oedematous, the proportion of water relative to the blood increases. The extravascular lung water volume (ELW) can be calculated using tracer techniques, by subtracting the volume of distribution of blood or plasma (V_p) from that of total water (V_w). In practice these volumes of distribution can be calculated by injecting intravenously a mixture of two indicators, one for water and one for plasma, and by sampling their dilution curves from a systemic artery (Chinard and Enns, 1954). This principle is well established for the measurement of overall pulmonary oedema (McCredie, 1974). However, as pointed out in a recent review (Chinard, 1975), there is still a need for a method for measuring *regional* extravascular lung water (rELW).

The use of γ-emitting tracers for water and plasma, which can be detected externally over the chest, represents a specific, non-invasive approach for measuring rELW. To this end, we have developed a technique which involves the intravenous injection of $^{113}In^m$ and water labelled with ^{15}O.

Theory

Following an intravenous injection of $H_2{}^{15}O$, its first passage through the lungs can be recorded by means of detectors placed externally over the chest. The volume of lung water (V_w) seen from an external detector is given by:

$$V_w = F . \bar{t}_w \qquad (1)$$

where F is local blood flow and $\bar{t}_w$ the mean transit time calculated from the experimental curve.

Following an intravenous injection of $^{113}In^m$, which binds instantaneously and irreversibly to plasma transferrin, the volume of plasma (V_p) seen from the detector is given by:

$$V_p = F . \bar{t}_p \qquad (2)$$

where $\bar{t}_p$ is the mean transit time of the plasma tracer.

The extravascular water within the lung region viewed by the detector (rELW) can then be calculated as the difference between the local water and blood pools:

$$\text{rELW} = V_w - V_p = F(\bar{t}_w - \bar{t}_p) \qquad (3)$$

To be meaningful, measurements of rELW have to be related to the amount of lung seen by the detector, ideally the tissue dry weight. An alternative approach can be used in which rELW is related locally to intravascular volumes and flows:

rELW per unit of blood volume: $\dfrac{(V_w - V_p)}{V_p}$

From equations (2) and (3) this equals: $\dfrac{\bar{t}_w - \bar{t}_p}{\bar{t}_p}$

rELW per unit of blood flow: $\dfrac{(V_w - V_p)}{F}$

From equation (3) this equals $\bar{t}_w - \bar{t}_p$

To obtain an absolute value for overall ELW, an independent measurement of cardiac output is required. A weighted average of $\bar{t}_w - \bar{t}_p$ between base and apex from the right lung can be obtained by allowing for regional differences in blood flow per unit of blood volume ($1/\bar{t}_p$) and in the volume of blood seen from the collimator (calculated from the value for the equilibrium level of $^{113}In^m$). The resulting weighted $\bar{t}_w - \bar{t}_p$ can be multiplied by the water content of the cardiac output (Goresky *et al.*,

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TABLE I

Cardiac output and pulmonary blood volume per square metre of body surface area in controls and patients as measured by the radiocardiographic technique

Controls			Patients		
Subject	Cardiac index l/min./m²	Pulmonary blood volume ml./m²	Subject	Cardiac index l/min./m²	Pulmonary blood volume ml./m²
CM	3·15	319	JS	1·49	274
FF	3·44	275	JM	1·20	234
MH	2·53	282	KB	1·94	336
PR	3·18	331	VK	2·77	355
GF	3·60	304	VK	2·19	304
DK	3·33	253	JML	1·75	339
DL	2·80	374	EP	2·70	238
			AD	2·22	346
			VG	1·98	277
			BE	1·92	329
			IJ	2·66	209
			LJ	3·27	261
Mean	3·15	305	Mean	2·17	292
S.D.	±0·12	± 40	S.D.	±0·59	± 50

TABLE II

Values for overall ELW (ml per square metre of body surface area) and for rELW in controls and patients

Controls						Patients					
	ELW/m² ml.	ELW/BL. Volume		ELW/BL. Flow			ELW/m² ml.	ELW/BL. Volume		ELW/BL. Flow	
		Base	Apex	Base	Apex			Base	Apex	Base	Apex
CM	88	0·36	0·34	1·95	1·99	JS*	139	0·76	0·71	6·81	5·93
FF	59	0·32	0·35	1·55	1·54	JM*	132	0·72	0·68	8·32	7·31
MH	62	0·25	0·33	1·58	1·97	KB*	132	0·80	0·71	5·48	4·36
PR	106	0·37	0·40	2·37	2·38	VK*	217	0·97	0·82	6·85	4·36
GF	117	0·55	0·53	2·37	2·22	VK*	161	0·95	0·74	5·81	4·42
DK	100	0·56	0·50	2·29	1·98	JML*	173	0·91	0·56	7·60	5·74
DL	77	0·31	0·39	1·85	2·14	EP	111	0·69	0·62	3·24	2·41
IS	—	0·28	0·27	2·27	2·18	AD	145	0·60	0·58	4·64	4·49
JS	—	0·38	0·33	2·38	2·30	VG	154	0·96	0·77	5·78	4·78
						BE	101	0·88	0·59	4·59	2·90
						IJ	53	0·47	0·34	1·61	1·07
						LJ	110	0·54	0·61	2·37	2·37
Mean	87	0·38	0·38	2·07	2·08	Mean	136	0·77	0·64	5·26	4·18
S.D.	±22	±0·11	±0·08	±0·34	±0·24	S.D.	±41	±0·17	±0·13	±2·07	±1·75

* = patients with radiological evidence of pulmonary oedema.

1971), in order to calculate ELW (using formula 3). It is assumed that ELW is distributed evenly between the right and the left lung and that there are no gross differences between the ratio of blood volume to alveolar volume (or dry tissue weight) in the upper and lower zones in the supine position.

Methods

We investigated nine normal volunteers and 11 ambulant patients with various diseases of the left heart, predominently of the mitral valve. One patient was studied twice, on admission to hospital and after ten days of therapy with diuretics. In nine of the patients routine cardiac catheterization was performed at a separate session. Radiological evidence of pulmonary oedema was independently assessed for each patient. Routine lung perfusion scans were obtained in all patients on a large field gamma camera following injection of $^{99}Tc^{m}$ labelled microspheres. Cardiac output and pulmonary blood volume were measured in all patients and seven of the normals by the radiocardiographic technique. (Donato *et al.*, 1962; Giuntini *et al.*, 1963). Lung

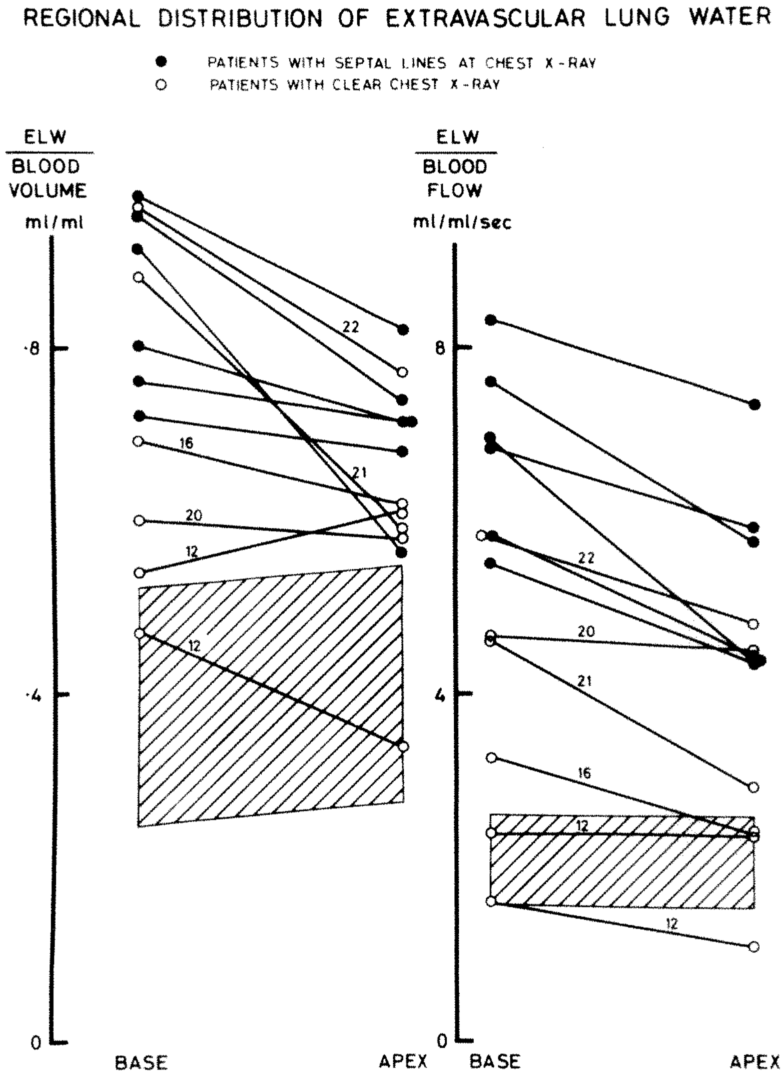

FIG. 1.

Regional distribution of extravascular lung water per unit of blood volume and blood flow.

rELW/blood volume (left) and rELW/unit blood flow (right) for two regions of the lung in patients with (●) and without (○) radiological evidence of interstitial pulmonary oedema. In the latter group of patients direct or indirect (mean pulmonary wedge pressure) measurements of the left atrial pressure are shown. Stippled area represents the normal range.

water studies were carried out with the subject in the supine position. Two collimated detectors were used with a separation of 8·5 cm., one over the upper zone and one over the lower zone of the right lung. Seven millicuries of a plasma tracer $^{113}In^{m}$ (100 minutes half-life, 390 kV) were injected through a percutaneous catheter with its tip in the superior vena cava and time activity curves recorded from the detectors on a multichannel analyser. After 45 to 60 seconds the same procedure was repeated using 15 mCi of water labelled with ^{15}O (2·1 minutes half-life, 510 keV) produced by the M.R.C. Cyclotron. The whole body absorbed radiation dose resulting from these combined injections is 0·2 rad. After completion of the procedure, mean transit times were calculated from the experimental time activity curves by extrapolating the downslope in order to eliminate recirculation.

RESULTS

Radiological evidence of interstitial pulmonary oedema (as assessed mainly by the presence of septal lines) was found in six patients.

No difference in perfusion between the left and right lung were found in any patient with the lung scan.

Table I shows cardiac index and pulmonary blood volume in controls and patients, as calculated from the radiocardiogram. The cardiac index is in general lower in patients with left heart diseases but there were no systematic differences in pulmonary blood volume between the two groups.

Table II shows the individual results for overall and regional ELW in control and patients. In normal subjects overall ELW was 172±54 (mean±SD) (87±22/m^2 of body surface area). In patients with radiological evidence of pulmonary oedema ELW/m^2 was 159±33 ml. and in patients with a clear chest X ray 112±36 ml. No differences in perfusion between the left and the right lung were found in any patient with the lung scan.

Regional data for ELW per unit of blood volume and flow are plotted in Fig. 1 for the upper and lower lung region, with the range of values found in normal subjects and symbols for patients with and without radiological evidence of interstitial pulmonary oedema. Whereas in normal subjects rELW per unit of blood volume and flow is uniform from base to apex (Table II), most of the patients showed an increase of both ratios above the normal range. This was more marked at the base of the lung, despite the absence, in some cases, of radiological evidence of pulmonary oedema.

In patients without radiological evidence of pulmonary oedema (open circles, Fig. 1) there was a striking correlation between the elevation of rELW/blood flow and rELW/blood volume and the level of left atrial pressure.

DISCUSSION

A technique for quantitative assessment of overall and regional extravascular lung water in man, using external monitoring of γ-emitting radioisotopes, is presented. The validity of substituting external counting for arterial sampling has been demonstrated by direct comparison of the two techniques in the supine anaesthetized dog (Fazio *et al.*, 1976). The value for overall ELW for normal subjects with this relatively non-invasive technique compare well with those previously obtained with arterial sampling (McCredie, 1974).

There have been no previous measurements of rELW in man. An absolute value for rELW requires an independent measurement of regional flow in absolute terms. This is not a trivial requirement because it must be related to the volume of tissue seen in the counting field. Some indication of tissue volume could be obtained by rebreathing an inert radioactive gas (for example, ^{13}N) to equilibrium, but a significant underestimation of tissue volume would occur in the presence of alveolar oedema or abnormalities of lung expansion. In addition these procedures would add significantly to the complexity of the technique especially for ill patients.

For these reasons, we devised the expression, rELW per unit of regional blood flow and volume. Such indices require only measurement of mean transit times of a vascular and a water indicator, without independent measurement of blood flow. Both indices appear to be elevated in patients with increased left atrial pressure, despite, in some cases, the absence of radiological signs of pulmonary oedema. The distribution of both rELW/blood volume and rELW/blood flow is uniform from base to apex in normals, but in patients it is preferentially increased at the lung bases. It should be emphasized that we studied only ambulant patients and that the patients were in the supine position for only 15 or 20 minutes before the lung water measurements were performed. This suggests that chronic interstitial oedema is somehow gravity dependent, although its gravitational redistribution is rather slow.

These regional measurements appear to be more sensitive for the detection of subclinical pulmonary oedema than overall determinations of ELW (see Table II). This is due in part to the better resolution inherent in regional measurements as well as to the way in which extravascular lung water has been expressed. What do the ratios rELW/blood flow and rELW/blood volume mean in physiological terms? Both might be raised or lowered by abnormal values for blood volume or blood flow alone. Indeed the separation between normal subjects and patients with left heart diseases for rELW/flow may partly be related to the observed lower values for cardiac output in the patients group (Table I). On the other hand, no systematic reductions in the overall pulmonary blood volume were found to account for the increase in rELW/blood volume in patients.

We believe that rELW/blood volume reflects actual changes in interstitial oedema more specifically than rELW/blood flow. The latter index probably reflects additional pathological changes in patients with left heart disease, namely the redistribution of local perfusion and the reduction in cardiac output. Together, these ratios provide new and more sensitive information for the understanding of changes in the lung arising from left heart disease.

ACKNOWLEDGMENTS

We thank Professor J. F. Goodwin, Dr. C. M. Oakley and Mr. D. D. Vonberg for their support, Mr. P. D. Buckingham for technical expertise and Mrs. Moira Stuart for typing this article.

Dr. Fazio was a Wellcome Trust research fellow on leave from CNR Laboratory of Clinical Physiology, Pisa, Italy, and this work was supported in part by Grant No. 73.00490.04 of the National Research Council of Italy.

REFERENCES

CHINARD, F. P., and ENNS, T., 1954. Transcapillary pulmonary exchange of water in the dog. *American Journal of Physiology*, *178*, 197–202.

CHINARD, F. P., 1975. Estimation of extravascular lung water by indicator-dilution techniques. *Circulation Research*, *37*, 137–145.

DONATO, L., GIUNTINI, C., LEWIS, M. L., DURAND, J., ROCHESTER, D. F., HARVEY, R. M., and COURNAND, A., 1962. Quantitative radiocardiography. I. Theoretical considerations. *Circulation*, *26*, 174–182.

FAZIO, F., JONES, T., JONES, H., RHODES, C. G., and HUGHES, J. M. B., 1976. External counting for measuring pulmonary oedema. *Journal of Nuclear Biology and Medicine* (in press.)

GIUNTINI, C., LEWIS, M. L., SALES LUIS, A., and HARVEY, R. M., 1963. A study of the pulmonary blood volume in man by quantitative radiocardiography. *Journal of Clinical Investigation*, *42*, 1589–1605.

GORESKY, C. A., CHINARD, F. P., CRONIN, R. F. P., and WANGEL, B. E., 1971. Extravascular water space. In: *Central Hemodynamics and Gas Exchange*, edited by C. Giuntini, pp. 449–458 (Minerva Medica, Torino).

McCREDIE, R. M., 1974. The measurement of lung water. In *Progress in Cardiology*, *3*, edited by P. N. Yu, and J. F. Goodwin, pp. 331–349 (Lea and Febiger, Philadelphia).

Book review

Atlas of Roentgenographic positions and standard Radiologic Procedures (three vols). By V. Merrill, pp. 1030 (illus.), 1975. Fourth edition (Published by Mosby Company, Saint Louis. Distributed in Great Britain by Henry Kimpton), £28·50.

These three volumes are the standard reference book in the United States of America on radiographic positioning. As such it is invaluable to radiologist, radiographers and radiography students. It compares fairly favourably with a book of similar objectives which we use in this country.

The presentation of the fourth edition is similar to that of the third—well bound and clearly set out. The general layout is little altered although there are some extra sections on more recently developed aspects of radiography. The photographs, regrettably, have not been brought up to date and still show very old fashioned equipment which students are not likely to encounter in their practical work. This makes it difficult for them to relate what they see in the book with what they do in practice. However the line drawings which accompany the photographs are most helpful and clearly drawn.

There is a detailed list of contents of all three volumes at the front of each volume and a brief list of sections on the outside of the cover which facilitates quick reference.

At the back of each volume there is an index and a bibliography of other books and papers written on the subjects contained within that volume. This is a very useful list for those who wish to enquire further into a subject or those who are lecturing. Volume I also has a glossary of medical terms some of which are, of course, spelt with American spelling or are American terms, but otherwise this is a useful section.

CHANGES AND ADDITIONS IN FOURTH EDITION

Volume I. Sections have been added on paediatric radiography, body section radiography and foreign body localization.

Volume II. No change.

Volume III. The chapter on the soft tissue neck now includes views for the thyroid. The chapter on the breast has been expanded but still does not include any mention of xeroradiography. The chapter on the central nervous system now includes stereotaxis and subtraction techniques.

There are new chapters on ultrasonography and thermography, nuclear medicine and its technology and also the principles of radiation therapy.

These additions bring the book up to date so that it is of more use as a modern reference book but it is surprising that no mention has been made of the new ideas being developed in America for electron radiography and related ideas and also of computerized transverse section scanners already in use both sides of the Atlantic by the time this new edition was printed.

The best part of this book is the relevant radiographic anatomy at the beginning of each section with excellent diagrams some of which are coloured.

The disadvantage for the English reader is the continued use of proper names to describe radiographic views, *e.g.* Water's view, Caldwell's view, etc. This makes the whole subject very confusing for those studying it for the first time. Some of the American terminology could also be confusing.

JENNIFER RICHMOND.

1976, *British Journal of Radiology*, *49*, 398–406

Angiographic changes following acute spinal cord compression: an experimental study in monkeys

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(*Received July, 1975*)

ABSTRACT

Acute paraplegia was produced in monkeys by abruptly inflating a balloon catheter within the epidural space. The arteriographic and epidural venous changes following such trauma were serially evaluated. Spinal-cord arteriograms following cord injury remained normal during an acute (four-hour) follow-up. Serial epidural venograms demonstrated obstruction of epidural veins within four hours at the site of contusion in less than half of the animals studied. Neither spinal arteries nor epidural veins showed consistent diagnostic changes following trauma due to acute epidural compression.

Key words

Spinal cord compression; spinal cord arteriography; epidural venography; spinal cord microangiography.

The patient with an acute spinal cord injury but without grossly dislocated vertebral elements presents a therapeutic problem. Emergency decompression may restore circulation to a severely contused cord in which rapidly accumulating oedema and focal haemorrhage are shutting off intrinsic circulation. However, a mild contusion of the spinal cord, often clinically indistinguishable in the early stages from a more severe injury, may not be benefited by laminectomy. In the past, myelographic demonstration of a block has been used as one of the parameters to select candidates for decompression. However, myelography in an acutely para- or tetraplegic patient is a technically difficult and potentially harmful procedure. Recently both DiChiro (Gargour *et al.*, 1972; Wener *et al.*, 1974) and Djindjian (Bussat *et al.*, 1973) have suggested that arteriography may have diagnostic value in assessing acute cord injury, and have presented their clinical experience with post-traumatic spinal-cord arteriography. However, there is little information about the *in vivo* response of *major* (or arteriographically demonstrable) arteries and veins in an acutely contused cord. Post-mortem perfusion studies of experimentally traumatized cords suggest that arteriographic alterations of the major spinal vessels will not be observed (Allen *et al.*, 1974; Assenmacher and Ducker, 1971; Ducker *et al.*, 1971; Fairholm and Turnbull, 1971; Fried and Goodkin, 1971).

For these reasons, the following study was undertaken to evaluate the acute arteriographic and venographic changes associated with compression injuries of the cord in monkeys.

MATERIALS AND METHODS

Fifteen Rhesus monkeys (4–8 kg) were basally sedated with phencyclidine hydrochloride* (1·0 mg/kg) and anaesthetized with frequently repeated intravenous doses of a short-acting barbiturate (sodium thiamylal†). Arterial and venous catheters were introduced by femoral cut-downs. Intravenous infusions of dextrose/water were administered throughout each study to maintain urine volume. Bladder distension was relieved periodically by transabdominal needle aspiration. All angiographic studies were magnified three times using a Dynamax 66A‡ tube with a 0·3 mm grid-biased focal spot.

The monkeys were divided into two groups, epidural venous studies (Group I) and spinal arterial studies (Group II). Cord injury in both groups was produced by abruptly and maximally (0·75 ml.) inflating the balloon of a 4 Fr Fogarty catheter§ within the upper lumbar spinal canal and maintaining inflation for ten minutes. The balloon was generally removed from the epidural space immediately following deflation. The technique for percutaneously introducing and positioning balloon catheters in the spinal canal of monkeys has been described in detail elsewhere (Doppman *et al.*, 1973). Following the injury and the acute angiographic studies, the animals were observed for 24 hours and their neurological status classified as (I) normal, (II) moderate weakness, *i.e.* unable to support weight but able to withdraw legs when stimulated, (III) spastic paraplegia, or (IV) flaccid paraplegia. This evaluation was based upon observation of the animals' activity in the cage and no attempt was made at detailed neurological testing. Angiographic studies were repeated at 24 hours, and the cord was

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then selectively perfused with opaque silicone rubber for microangiography. The thoracolumbar vertebral column was removed, fixed for seven to ten days in formalin, and the cord was removed through an extensive laminectomy. Microradiography was performed on a Faxitron 805 unit using mammographic (RPM, Kodak) film.

Group I—epidural venous studies

Control epidural venograms were obtained in nine monkeys by injecting meglumine iothalamate* (3 ml./second ×2) into the distal IVC below an occluding balloon catheter. Excellent filling of the lumbar and lower thoracic epidural venous plexus is consistently produced by this technique. Lateral serial venograms (one film/second ×6) were obtained in all monkeys; antero-posterior studies were performed in five. The cord was then acutely compressed at the L1–L2 level with an anterior (four monkeys) or lateral (three monkeys) epidural balloon. Venograms were obtained in all animals while the balloon was distended. Following deflation and removal of the balloon, venography was repeated at five and/or 30 minutes, two hours and four hours post-injury. At 24 hours, motor function was evaluated and the severity of paraplegia was graded. Epidural venography was repeated. An arterial catheter was then introduced, selective spinal cord arteriography was performed, and the cord was perfused for microangiographic studies.

In two control monkeys, the Fogarty balloon catheter was introduced into the spinal canal at the L1–L2 level, but the balloon was never inflated. Serial epidural venograms at half, one, two and four hours were performed, and the animals were clinically evaluated at 24 hours.

Group II—arterial studies

In five monkeys, control spinal cord arteriography was performed by injecting 2 ml. of methylglucamine iothalamate into the appropriate lumbar artery, usually L2. Lateral filming was carried out for 12 seconds to record the arterial, capillary and venous phases of the spinal-cord circulation. The cord was acutely compressed and selective serial spinal-cord arteriograms were obtained at five minutes, 30 minutes, one, two and four hours post-injury. The catheter remained in the selective lumbar artery throughout the study and was periodically perfused with heparinized saline. At 24 hours, the presence and severity of paraplegia were recorded, the animals were anaesthetized and spinal cord arteriography was repeated prior to perfusion and sacrifice.

In two animals the appropriate lumbar artery was selectively catheterized and spinal-cord arteriography was performed at five and 30 minutes, one, two and four hours, but a balloon catheter was not inflated in the epidural space. As in the cord injury group, the selective catheter was left in the lumbar artery and periodically perfused with heparinized saline throughout the four hour period.

RESULTS

Epidural venous studies

The results of the epidural venous studies are summarized in Table I.

In monkeys 1 and 2 undergoing serial epidural venography with catheter placement but without balloon inflation (Fig. 1), no neurological defects were observed at 24 hours.

In the cord injury group, the acutely inflated balloon appeared to completely fill the spinal canal (Fig. 2A). Venography during the period of balloon inflation demonstrated either complete non-filling of the epidural plexus (two monkeys) or obstruction to craniad flow at a variable distance below the balloon

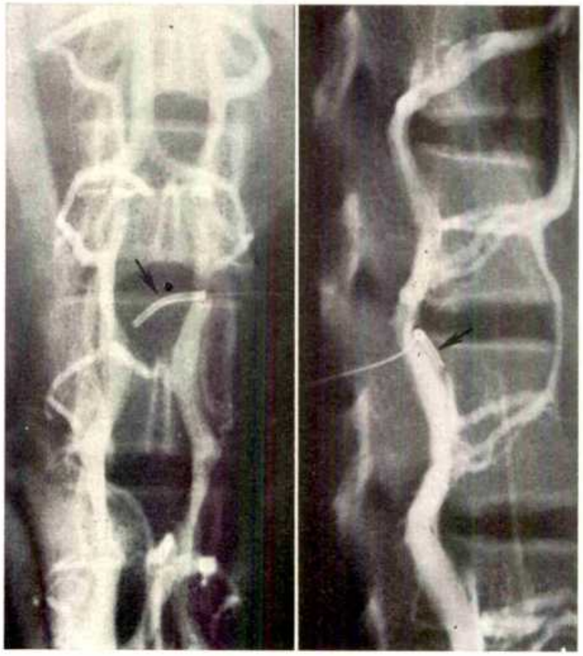
A B

FIG. 1.

Antero-posterior (A) and lateral (B) epidural venograms with the balloon catheter (arrow) in position but not inflated.

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*Conray 60, Mallinckrodt Chem Works, St. Louis, Missouri.

TABLE I

EPIDURAL VENOGRAPHIC STUDIES

Monkey	Site and size† of balloon	Severity of paraplegia	Venography	Arteriography 24 h	Microangiography
1 Control	Anterior L1–L2 Not inflated	Normal	Normal 5′, 30′, 60′ Normal 4 and 24 h	Not done	Not done
2 Control	Anterior L1–L2 Not inflated	Normal	Normal 5′, 30′, 60′ Normal 4 and 24 h	Not done	Not done
3	Anterior L1–L2 26 × 23 mm	Flaccid Grade IV	Normal 5′, 60′, 120′ Obstructed 4 and 24 h	Poor filling of posterior veins	Poor perfusion of central grey matter at and below balloon
4	Anterior T12–L1 22 × 22 mm	Flaccid Grade IV	Normal 30′, 60′ Obstructed 2, 4 and 24 h	Normal	Normal
5	Anterior L1–L2 18 × 22 mm	Flaccid Grade IV	Normal *30′, 120′ Normal *4 and 24 h	Normal	Normal
6	Anterior L1–L2 18 × 23 mm	Flaccid Grade IV	Normal *5′, 120′ Normal *4 and 24 h	Normal	Normal
7	Lateral L1–L2 19 × 20 mm	Spastic Grade III	Normal 30′, 60′, 120′ Normal 4 and 24 h	Normal	Normal
8	Lateral L1–L2 20 × 21 mm	Spastic Grade III	Normal *5′, 120′ Normal 4 and 24 h	Normal	Normal
9	Lateral T12–L1 23 × 23 mm	Paretic Grade II	Normal 30′, 120′ Obstructed 4 h Normal 24 h	Normal	Technically inadequate perfusion

*Unilateral focal obstruction of epidural vein at intervertebral foramen through which epidural balloon was introduced
†Not corrected for magnification.

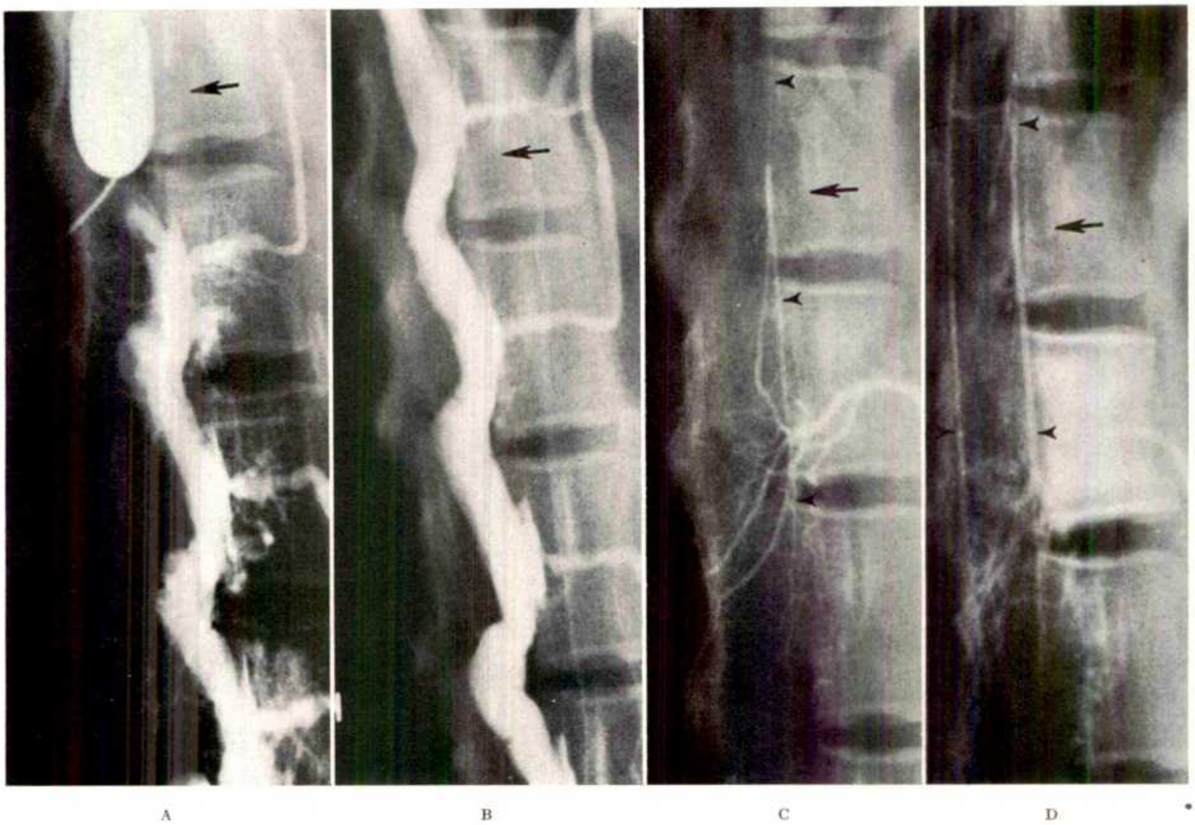
(Doppman, 1974; 1975). Thus, all acutely-inflated balloons produced total obstruction of the epidural venous plexus.

Following deflation and removal of the balloon, the immediate (five-minute or 30-minute) venograms were normal in five (Fig. 2). Unilateral localized non-filling of the epidural vein at the foramen through which the balloon catheter was introduced (always left L1–L2) was observed in three monkeys. Probably a post-traumatic change due to catheter introduction, this localized obstruction cleared on the two-hour film in one instance (Monkey 8) but persisted in the other two (Monkeys 5 and 6) and was ignored when evaluating serial progressive venographic changes. No acute extravasation of contrast media suggesting venous haemorrhage was demonstrated.

In two monkeys, progressive obstruction of the epidural veins at the level of injury (Figs. 3 and 4) developed.

All monkeys were paralysed at 24 hours. The severity of paraplegia appeared to be related to the site of the balloon at the time of inflation (Doppman, in press; Ramsey and Doppman, 1973). Balloons directly in front of the cord (Monkeys 3–6) produced the most severe neurological deficit: all had Grade IV or total flaccid paraplegia and two of them showed progressive epidural venous obstruction. Lateral epidural balloons (Monkeys 7–9) were associated with less severe neurological deficits—spastic paraplegia (Grade III) in two and inability to stand (Grade II) in one. Only one of these showed evidence of epidural obstruction on the four-hour film with reversion to normal at 24 hours.

All seven monkeys had normal selective spinal cord arteriograms at 24 hours except for a single Grade IV paraplegic monkey with absent filling of veins on the posterior cord surface. This same monkey was one of two showing progressive obstruction of the epidural venous plexus on the four- and 24-hour venograms (Fig. 4C). Microangiography in this monkey revealed cord swelling and poor perfusion of the arteries to the central grey matter at balloon level (Fig. 4D). The microangiographic studies of the remaining cords appeared normal.



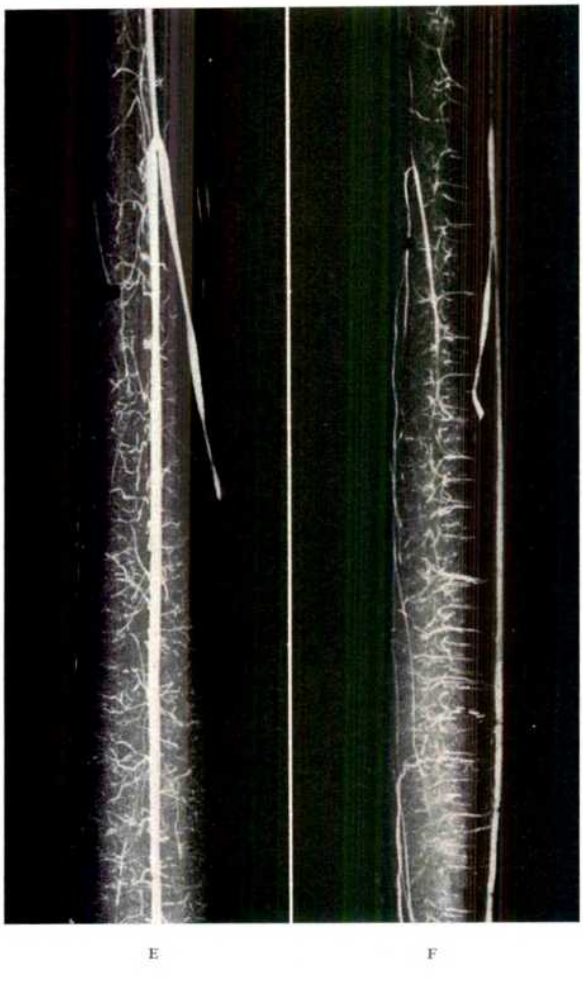


Fig. 2.

(A) Inflated lateral balloon at L1 completely obstructs epidural veins. Note congested tense appearance of obstructed veins (A) compared with normal (B). Large arrow on this and subsequent radiographs marks site of cord injury.

(B) Normal 24-hour venogram. All post-injury venous studies were normal.

(C and D) Twenty-four hour arteriograms, arterial and venous phases. No displacement of anterior spinal artery (arrowheads) and no swelling of cord on venous phase.

(E and F) Microradiographs show no evidence of non-filling, extravasation or cord swelling. Arrowheads indicate site of contusion. Animal had spastic paraplegia (Grade III) following injury.

TABLE II

Arteriographic studies

Monkey	Site of balloon	Severity of paraplegia	Arteriography	Microangiography
1	Not inflated L1–L2	Flaccid* Grade IV	Normal 5′, 30′, 60′ Normal 2 and 4 h	Not performed
2	Not inflated L1–2	Flaccid* Grade IV	Normal 5′, 30′, 60′ Normal 2 and 4 h	Not performed
3	Anterior L2–3	Flaccid Grade IV	Normal 30′, 60′ Cord focally swollen 2, 4 h Nonfilling of posterior veins, 24 h	Poor filling of central vasculature. ASA normal
4	Anterolateral L1–2	Flaccid Grade IV	Normal 5′, 30′, 60′ Normal 2, 4 h Prolonged ASA filling 24 h	Cord swollen, poor filling of central vessels
5	Anterior L1–2	Flaccid Grade IV	Normal 5′, 30′, 60′ Normal 2, 4 h Technical failure, 24 h	Cord swollen, sulcal arteries not well filled
6	Posterior L1–2	Died evening of study	Normal 30′, 60′ Normal 2, 4 h	Normal

*Paraplegia due to arteriography, see text.

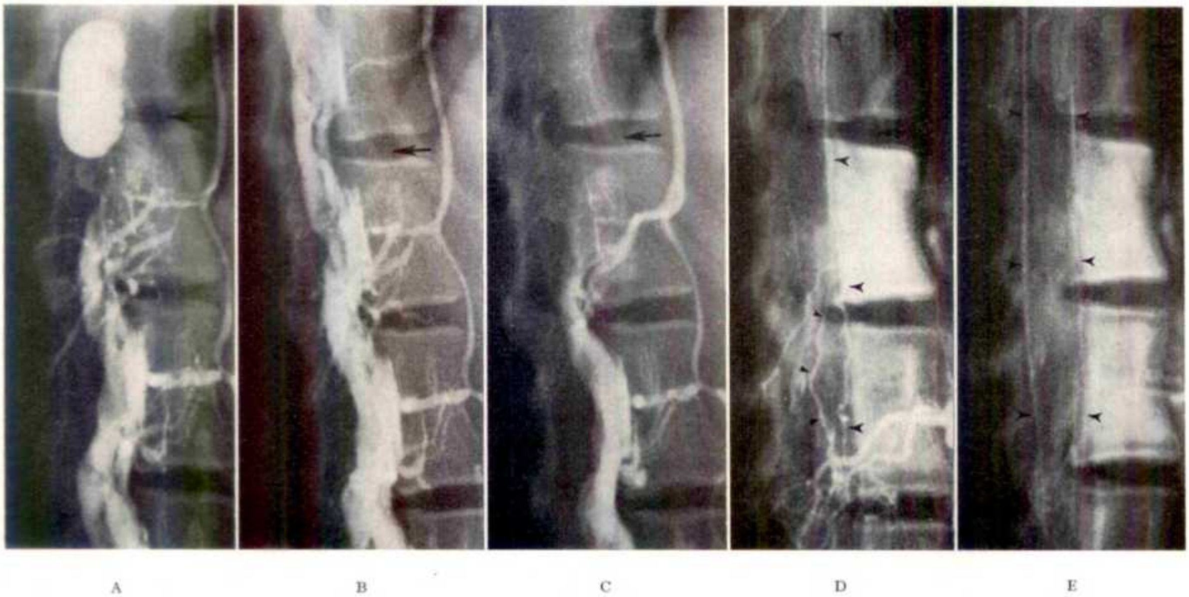


Fig. 3.

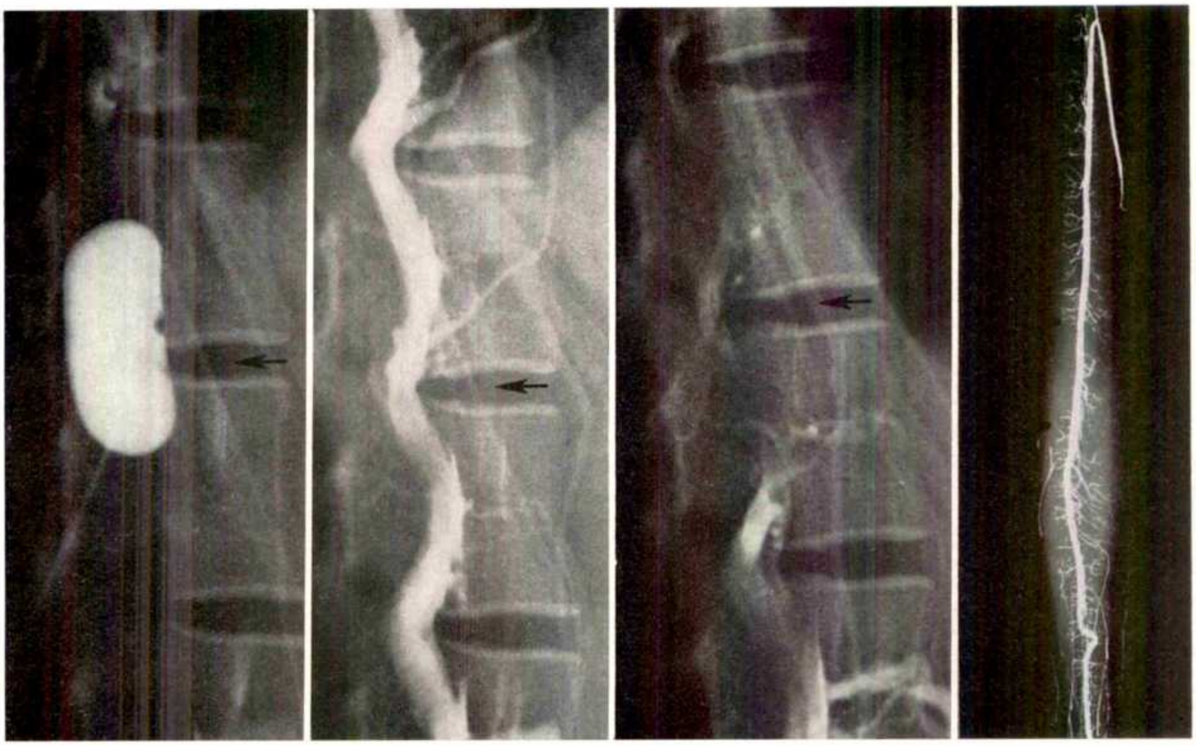
(a) Inflated anterior balloon at T12–L1 level totally obstructing epidural veins.

(b) Thirty minutes post-injury; normal epidural venogram.

(c) Two-hour venogram shows development of total obstruction just below site of balloon injury. Obstruction persisted on four and 24-hour films.

(d) Selective L-2 arteriogram, at 24 hours; artery of Adamkiewicz (small arrow-heads) and anterior spinal artery (large arrow-heads) appear normal, especially at site of balloon contusion (large arrow). Opacified 1st lumbar vertebra resulted from preceding injection.

(e) Venous phase of spinal cord arteriogram outlines anterior and posterior surface of cord (arrow-heads). Note absence of gross cord swelling at site of compression (large arrow). Microangiography was normal.



A B FIG. 4. C D

(A) Venogram with inflated epidural balloon at L1–L2. Note total non-filling of epidural venous plexus.

(B) Two hours post-injury; venogram remains normal.

(C) Twenty-four hour venogram reveals obstructed epidural veins at inferior margin of L2. Arteriogram revealed poor filling of posterior veins at level of injury.

(D) Microradiograph of perfused anterior spinal artery. Note decreased filling of central arteries at site of balloon contusion between arrowheads.

Arterial studies

Table II summarizes the results in this group of animals.

The two control monkeys undergoing serial selective spinal cord arteriography without balloon injury were paraplegic (Grade IV) at 24 hours. All acute arteriograms were normal in these two animals. Arteriography at 24 hours showed prolonged arterial opacification and absent venous filling.

In the cord injury group there were three anterior balloons and one posterior balloon. Arteriography during balloon inflation showed obstruction of the anterior spinal artery in two, and displacement without obstruction in two.

Serial selective spinal cord arteriograms during the four hours following removal of the balloon remained normal. The anterior spinal artery showed no evidence of spasm or displacement on studies performed within five minutes of deflating and removing the balloon. Antero-posterior cord diameters at the site of balloon trauma were serially measured over four hours and, even with the advantage of a pre-injury control, cord swelling was observed only once (Fig. 5). Neither prolonged opacification of the anterior spinal artery nor delayed filling of the posterior spinal veins were observed on the acute (up to four hours) arteriographic studies.

One animal from this group expired the evening of the experiment from excessive femoral bleeding. A 24-hour arteriogram could not be performed but the cord was normal on a post-mortem microangiographic study. The three remaining animals were severely paraplegic (Grade IV) at 24 hours. Twenty-four hour spinal cord arteriograms showed prolonged opacification of the anterior spinal artery and delayed or absent filling of the posterior spinal veins (Fig. 5D). Microangiograms of perfused cords

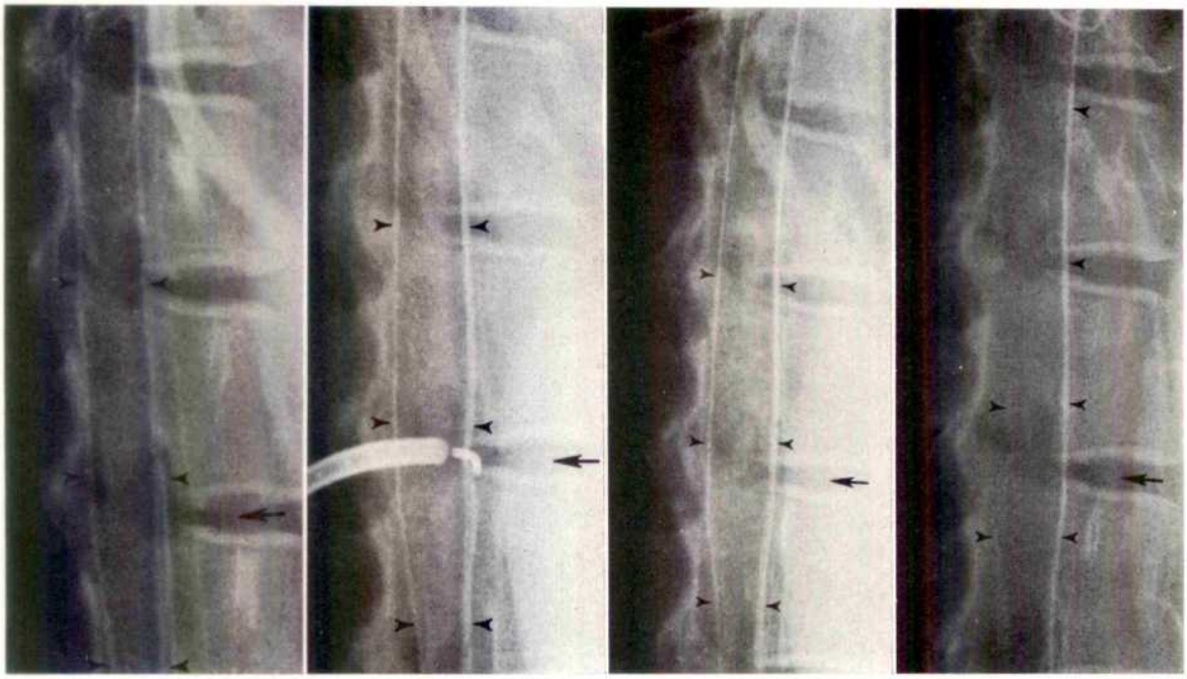


Fig. 5.

(A) Control arteriogram, venous phase; cord well outlined (arrow-heads) by anterior and posterior veins. Large arrow indicates site of contusion.

(B) Thirty minutes post-balloon contusion; deflated balloon catheter still in position.

(C) Four hours post-injury. Cord slightly but diffusely swollen. Posterior veins are thinned and displaced against lamina.

(D) Twenty-four hour study, 15-second film. Anterior and posterior spinal arteries (arrow-heads) remain filled for a prolonged period but the spinal veins never filled.

showed normal filling of the anterior spinal artery but poor perfusion of the sulcal arteries and the central grey matter.

Discussion

Our technique for acutely contusing the cord differs from the classic Allen method in which weights are dropped a known distance onto the posterior surface of the surgically exposed cord. We chose to use an abruptly inflated balloon introduced percutaneously into the epidural space in order to avoid a laminectomy which might influence the haemodynamics of the spinal and epidural vessels in the post-injury period. Other investigators have used a similar technique for cord injury studies (Thienprasit *et al.*, 1975; Martin and Bloedel, 1973; Tarlov, 1957).

These preliminary studies suggest that epidural venography may be of some clinical value in the early stages for selecting acutely paraplegic patients likely to benefit from decompression. In two of four animals with the most severe (Grade IV) paraplegia, the development of epidural venous obstruction during the four hours post-injury suggests progressive cord and peridural swelling sufficient to fill the spinal canal and interfere with local perfusion. The venous obstruction occurred at a stage when arteriography was always normal in a similarly injured group of animals. Myelographic block was probably also present at this time but was not investigated. A study is currently under way to compare myelographic and venographic findings in a group of acutely paraplegic animals to establish the sensitivity of each diagnostic test as an indicator of complete block.

However, obstruction of epidural veins did not appear to be a very *sensitive* indicator of cord trauma, being observed in only half of the most severely paralysed animals and in none with lesser degrees of paraplegia.

Even more disappointing was the absence of arteriographic changes during the immediate post-injury phase. Neither spasm nor displacement of the anterior spinal artery were observed on immediate or serial (up to four hours) arteriograms. Focal swelling at the site of cord injury could not be diagnosed on serial measurements of the cord's antero-posterior diameter, even with the availability of pre-injury measurements. Although sulcal arteries in the monkey spinal cord can be faintly visualized on magnified normal lateral angiograms, extravasation of contrast into the grey matter was never observed. (Microradiographic studies of paraplegic monkeys traumatized by the Allen technique usually show extravasation at four hours). These findings in the Group II (serial arteriogram) monkeys were supported by the normal 24-hour arteriograms and microangiograms in all Group I (serial venogram) monkeys.

The Group II studies might be criticized on the basis that serial arteriography over four hours with an indwelling selective catheter produces spinal cord injury and paraplegia without the additional trauma of an epidural balloon. Repeated injection of contrast media and reduced arterial inflow probably both contribute to the cord injury. (An embolic aetiology seems unlikely in view of the normal serial arteriograms.) However, repeated venographic studies do not injure the cord and we knew from the Group I study that balloons of this diameter at this level always produced paraplegia. There seemed to be no alternate way to evaluate acute arteriographic changes than to perform serial arteriography. Removing the catheter from the lumbar artery between injections might have lessened the incidence of post-arteriographic paraplegia, but lumbar arteries in monkeys are prone to spasm and repeated catheterizations may be difficult. The fact that the spinal cord arteriograms remained normal up to four hours suggests that neither acute cord compression, contrast media injury, nor the combination of insults produces diagnostic arteriographic findings in the acute phase.

The role of arteriography in the evaluation of spinal cord injury has yet to be determined. Total obstruction or transection of the anterior spinal artery can be demonstrated by arteriography but is uncommon except in penetrating injuries. Under such circumstances, the clinical evidence for cord disruption should be sufficient. Compression of the cord by fracture fragments or haematomas could be diagnosed arteriographically by displacement of the anterior spinal artery but similar information would be available myelographically. It is the acutely paraplegic patient with a negative myelogram that vexes the neurosurgeon, and in these acute contusions arteriography in the early post-injury phase will probably contribute little information upon which to base a prognosis or a decision to decompress. The use of arteriography in dorso-lumbar vertebral fractures to identify the level of the artery of Adamkiewicz prior to anterior decompression is a separate application, not restricted to trauma, originally recommended by us (Doppman *et al.*, 1968) and recently re-emphasized by Bussat *et al.* (1973).

Epidural venography is more informative and probably less harmful than spinal arteriography in cases of acute traumatic paraplegia. We have demonstrated obstructed epidural veins at the level of a contused cord and in the presence of a normal spinal cord arteriogram. But its sensitivity as an indicator of acute cord injury must be evaluated against the diagnostic value of myelographic and neurophysiologic (evoked cortical potential) studies.

Acknowledgment

Miss Mary Girton and Mr. R. Diggs provided excellent technical assistance. Manuscript preparation was supervised by Jeanette Hayes.

REFERENCES

Allen, W. E., III, D'Angelo, C. M., and Kier, E. L., 1974. Correlation of microangiographic and electrophysiologic changes in experimental spinal cord trauma. *Radiology*, *111*, 107–115.

Assenmacher, D. R., and Ducker, T. B., 1971. Experimental traumatic paraplegia. The vascular and pathological changes seen in reversible and irreversible spinal cord lesions. *Journal of Bone and Joint Surgery*, *53-A*, 671–680.

Bussat, P., Rossier, A. B., Djindjian, R., Vasey, H., and Berney, J., 1973. Spinal cord angiography in dorsolumbar vertebral fractures with neurological involvement. *Radiology*, *109*, 617–620.

Doppman, J. L., 1974. The effect of intraspinal masses on flow in the epidural venous system. An angiographic study in monkeys. *Investigative Radiology*, *9*, 74–81.

1975. The mechanism of Ischemia in antero-posterior compression of the spinal cord. *Investigative Radiology*, *10*, 543–551.

Doppman, J. L., DiChiro, G., and Morton, D. L., 1968. Arteriographic identification of spinal cord blood supply prior to aortic surgery. *J.A.M.A.*, *204*, 174–175.

Doppman, J. L., Ramsey, R., and Thies, R. J., 1973. A percutaneous technique for producing intraspinal mass lesions in experimental animals. *Journal of Neurosurgery*, *38*, 438–447.

Ducker, T. B., Kindt, G. W., and Kempe, L. G., 1971. Pathological findings in acute experimental spinal cord trauma. *Journal of Neurosurgery*, *35*, 700–708.

Fairholm, D. J., and Turnbull, I. M., 1971. Microangiographic study of experimental spinal cord injuries. *Journal of Neorosurgery*, *35*, 277–286.

Fried, L. C., and Goodkin, R., 1971. Microangiographic observation of the experimentally traumatized spinal cord. *Journal of Neurosurgery*, *35*, 709–714.

Gargour, G. W., Wener, L., and DiChiro, G., 1972. Selective arteriography of the spinal cord in post-traumatic paraplegia. *Neurology*, *22*, 131–134.

Martin, S. H., and Bloedel, J. R., 1973. Evaluation of experimental spinal cord injury using cortical evoked potentials. *Journal of Neorosurgery*, *39*, 75–81.

Ramsey, R., and Doppman, J. L., 1973. The effects of epidural masses on spinal cord blood flow. *Radiology, 107,* 99–103.
Tarlov, J. M., 1957. *Spinal Cord Compression; Mechanisms of Paralysis and Treatment* (Charles Thomas Publishers, Springfield, Illinois).
Thienprasit, P., Bantli, H., Bloedel, J. R., and Chou, S. N., 1975. Effect of delayed local cooling on experimental spinal cord injury. *Journal of Neurosurgery, 42,* 150–154.
Wener, L., DiChiro, G., and Gargour, G. W., 1974. Angiography of cervical cord injuries. *Radiology, 112,* 597–604.

Book review

Venous Thrombo-embolic Disease. pp. 255, 1975 (Churchill Livingstone), £5·00.

Thrombo-embolic disease remains a topical subject, and this book records the proceedings of a symposium held at the University of Edinburgh in September 1974 at which the subject was thoroughly reviewed by a distinguished group of contributors. The stated objectives were "to provide an opportunity for workers in this field to report on their current research interests . . . and to obtain authoritative views on clinical management". Accordingly, the book is split into sections dealing with prophylaxis, research papers and pulmonary embolism, which comprises the bulk of the material presented. Most papers are in the form of reviews of the authors' published work, and not much new information is presented. The advances made in this field in the past ten years have been so considerable that it is wise to take stock of the situation and objectively assess the changes that have resulted in routine hospital practice. The physiological studies on the determinants of femoral-vein blood flow by Cotton and his colleagues are noteworthy in this respect, in that they confirm the importance of venous stasis during surgical operations in the genesis of venous thrombosis. V. V. Kakkar gives a clear account of the use of low-dose Heparin in routine surgical practice in several centres, and describes its limitations. The recent general tendency towards earlier ambulation of medical and surgical patients may well be influencing the natural history of venous thrombosis, although as Macpherson points out in his opening remarks, the occasional dramatic death from pulmonary embolism is not prevented. Of interest to radiologists particularly are the papers by Buist on peripheral phlebography with comments by Lea Thomas, and by Miller on the assessment of fibrinolytic therapy for massive pulmonary embolism by pulmonary angiography. P. K. Caves contributes a comprehensive review of pulmonary embolectomy, stressing the current low mortality when cardiopulmonary bypass is used. The use of "flying squads" for the surgical treatment of pulmonary embolism has not been without problems, and the consensus view is that transport to a centre with full facilities for cardiopulmonary bypass is more satisfactory.

Many fascinating problems remain to be unravelled in the field of venous thrombo-embolism, but the application of scientific methods, including controlled trials of therapy, has undoubtedly contributed to a clearer understanding of this very common problem. This book is compact and comprehensive, and the editors and publishers are to be congratulated on the short time which has elapsed from the time of the symposium to publication. I would recommend the book as a good buy both for those interested in gaining an overall view of the "state of the art" and also to those who have deeper interests in this field, as a handy reference source.

R. Wray.

1976, *British Journal of Radiology*, *49*, 407–415 MAY 1976

Arteriography in bone tumours

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(*Submitted July, 1975*)

ABSTRACT

The usefulness of arteriography in the diagnosis and management of bone tumours has been evaluated in 78 cases (49 malignant neoplasms, 17 benign tumours and 12 inflammatory lesions). Using well-defined criteria, of which the presence or absence of tumour vessels is of decisive importance, arteriography represents—not as a routine procedure but in selected cases—a most useful guide to establishing the diagnosis, by adding important information to standard radiography, by defining the extent of the lesion and by assisting in the selection of the best site for biopsy.

Although arteriography is a well-established radiologic method for the investigation of intracranial, intrathoracic and intra-abdominal organs, it has not gained wide acceptance in the diagnosis and management of bone tumours. In particular, there is much controversy about its usefulness in differentiating between benign and malignant disease, its role being limited to define the soft-tissue extent of bone tumours and to depict the appropriate site for biopsy (Feldman) *et al.*, 1975; Halpern and Freiberger, 1970; Viamonte *et al.*, 1973; Yaghmai *et al.*, 1971).

The lack of characteristic clinical symptoms renders radiology a crucial component of bone-tumour diagnosis. The radiologist has attempted to justify this decisive role through systematic analysis of the pathologic changes observed on conventional radiographs (Lodwick, 1971). In spite of a high degree of diagnostic accuracy obtained in this manner, the radiologic findings need histologic proof. However, the attempt to obtain the maximum diagnostic information from the radiographic studies is especially important, since the histologic diagnosis may also be subject to error. On the one hand, the tumour tissue is often quite inhomogeneous, while, on the other hand, the biopsy consists of only a portion of tissue (Johnson, personal communication; Uehlinger, 1974). It is, therefore, understandable that errors in predicting tumour aggressiveness, and even in establishing histologic type, cannot be avoided by the pathologist. Bone pathologists, therefore, hesitate to make a diagnosis without reviewing the radiographs. Since conventional radiography, including computerized analysis, has certainly achieved its maximum yield of information, the remaining frequency of error might further be reduced by adding arteriography to the conventional radiologic investigation.

The purpose of this paper is to analyse the usefulness of bone tumour arteriography, with special reference to the differentiation between benign and malignant neoplasms, tumour extent and prediction of histologic type.

MATERIAL AND METHODS

Our own experience with arteriography in neoplastic and inflammatory lesions of bones and soft tissues, starting in 1967, has up to now been based upon 93 cases, 50 per cent of which have been collected during the last two years (Table I). Of the total number of cases examined 15 (seven soft-tissue sarcomas, four benign tumours and four abscesses) were purely extraosteal in location and are, therefore, not included in this paper. The present evaluation is limited to lesions involving bone. All cases are histologically proven, either by open biopsy or after surgical removal.

Procedure

In each case arteriography was carried out using a red Odman-Ledin catheter (Kifa, Sweden; ID/OD 1·4/2·2 mm) with two side-holes 1 cm from the tip. With a manipulator instrument (Cook, Inc., Bloomington, Ind., U.S.A.) the tip of the catheter was always placed as close as possible to the disease process. The total amount of contrast medium (Urografin 76 per cent, Schering, West Germany) injected with a pressure injector apparatus (Contraves, Zürich, Switzerland), and the flow-rate were chosen depending on the diameter of the selectively catheterized artery, varying from 15 to 40 ml. at a rate of 5–15 ml./second. Exposures were made two per second for three seconds, one per second for six seconds and one every other second for eight seconds. As a rule, the disease process was investigated in at least two different projections. Magnification- and pharmacoangiography were not used, but in each case subtraction films were obtained.

TABLE I

Angiography in bone tumours 1967–1975

	Totally
Malignant tumours	
Osteogenic sarcoma	13
Chondrosarcoma	6
Malignant giant-cell tumour	2
Ewing-sarcoma	8
Reticulum cell sarcoma	1
Fibrosarcoma	4
Adamantinoma	1
Soft-tissue sarcoma with skeletal involvement	6
Soft-tissue sarcoma without skeletal involvement	7
Metastatic tumours in bone	8
	56
Benign tumours	
Osteochondroma	4
Osteoid osteoma	2
Benign chondroblastoma	1
Chondroma	1
Chondromyxoid fibroma	2
Giant-cell tumour	1
Fibroma	1
Haemangioma	2
Eosinophilic granuloma	2
Fibrous dysplasia	1
Soft-tissue tumours without skeletal involvement	4
	21
Inflammatory lesions	
Osteomyelitis	11
Soft-tissue abscesses	4
Villonodular synovitis	1
	16
Total	93

TABLE II

Malignant bone tumours

Specific signs	Neovascularity Tumour vessels—irregular calibre —distorted course —abrupt angulations Lakes Arteriovenous shunting
Non-specific signs	Hypervascularity Accumulation of contrast ("tumour stain") Early venous drainage

TABLE III

Benign Bone Tumours

Specific signs	Vascular displacement Absence of tumour vessels Absence of lakes
Non-specific signs	Hypervascularity Accumulation of contrast (parenchymal stain) Early venous drainage

TABLE IV

Osteomyelitis

Specific signs	Hypervascularity Accumulation of contrast (blush, stain) Early venous drainage
	Absence of tumour vessels

Evaluation

In analysing the usefulness of arteriography in tumours we concluded there were three main questions to be answered: does arteriography yield increased information over standard radiography in regard to:

(1) the differentiation between benign and malignant;

(2) the extent of the disease process;

(3) the prediction of histologic type?

The differentiation between benign and malignant neoplasms, as well as inflammatory lesions, was undertaken by using specific angiographic criteria (Tables II to IV). Thus, the diagnosis of a malignant neoplasm was based upon the presence of tumour vessels (characterized by an irregular calibre, a distorted course and abrupt angulations), vascular lakes and arteriovenous shunts within portions of the tumour (Fig. 1). In the absence of these signs of malignancy the lesion was called benign. Hypervascularity (dilated feeding arteries, increased number of regular shaped vessels within the disease process), accumulation of contrast medium during the capillary phase (parenchymal stain) as well as early venous drainage from the entire region involved were considered as non-specific (Fig. 2).

Results

1. *Differentiation between benign and malignant disease*

From a total of 49 malignant bone tumours unequivocal evidence of malignancy was present on the standard radiograph in 38 cases, whereas the other 11 cases could not be classified (Table V). Thirty-seven of the 38 cases diagnosed as malignant by

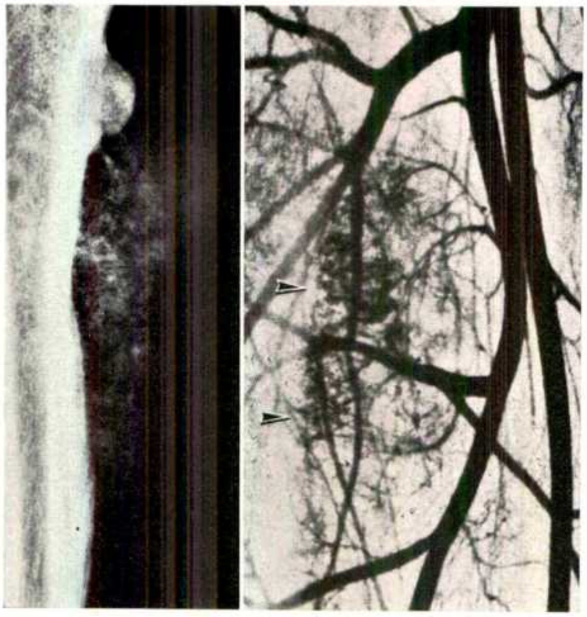

FIG. 1.

Female, 15 years. *Ewing's sarcoma* proximal shaft of femur. Tumour vessels (▶).

TABLE V

MALIGNANT BONE TUMOURS

				Total
Conventional radiography		38 positive	11 non-diagnostic	49
Angio-graphy	Positive	37	8	45
	Negative	1	3	4

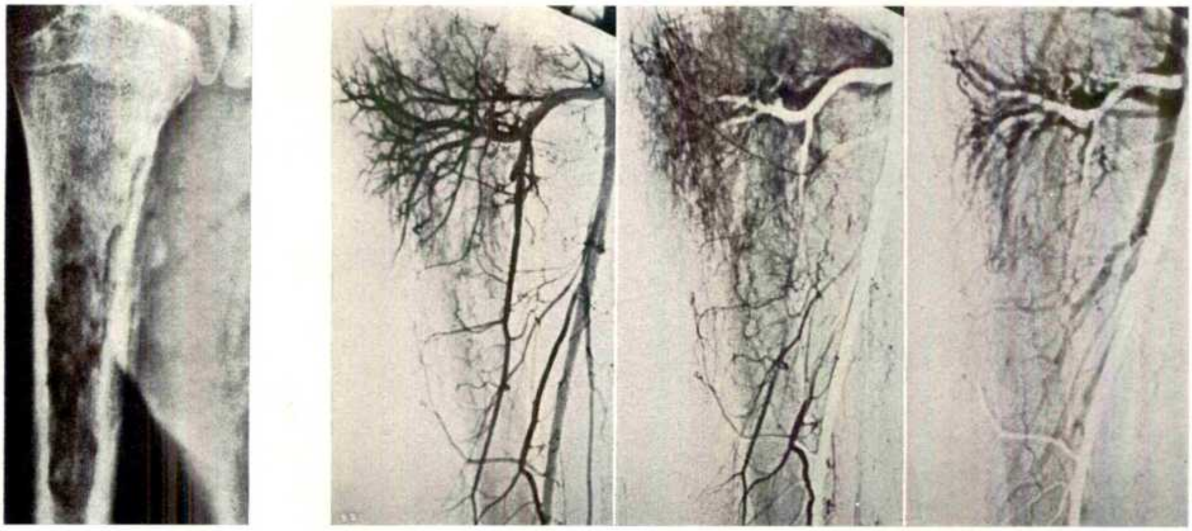

FIG. 2.

Male, 16 years. *Osteomyelitis.* Hypervascularity (dilated feeding arteries, increased number of regular shaped vessels), accumulation of contrast medium during capillary phase, early venous drainage from entire region involved. On plain film differentiation from malignant tumour not possible.

conventional radiography, also revealed the signs of malignancy angiographically; one parosteal osteogenic sarcoma, however, was totally avascular. Eight of the 11 non-diagnostic cases by standard techniques turned out to be malignant by arteriography (Fig. 3), whereas three cases (one fibrosarcoma, one adamantinoma, one Ewing's sarcoma) remained unclear after arteriography, because the specific signs of malignancy were lacking. Among the 17 benign bone tumours there were three cases, which were suspected to be malignant by standard radiography (one fibroma, one osteochondroma, one eosinophilic granuloma). In none of these 17 cases, however, was there any evidence of malignancy on arteriography (Fig. 4). Four cases of osteomyelitis, which could not be unequivocally differentiated from a malignant bone tumour by conventional radiography, revealed angiographically only a non-specific hypervascularity, as did seven further cases of clear-cut osteomyelitis (Fig. 5).

2. *Determination of tumour extent*

For exact delineation of tumour extent arteriography was especially valuable in malignant bone tumours which have grown out into the soft tissues (Fig. 6). In these instances, the full size of the tumour, as seen on arteriography, exceeded its overall extent, determined by standard radiography, in osteogenic sarcoma, Ewing's sarcoma and reticulum-cell sarcoma by one-third; in malignant

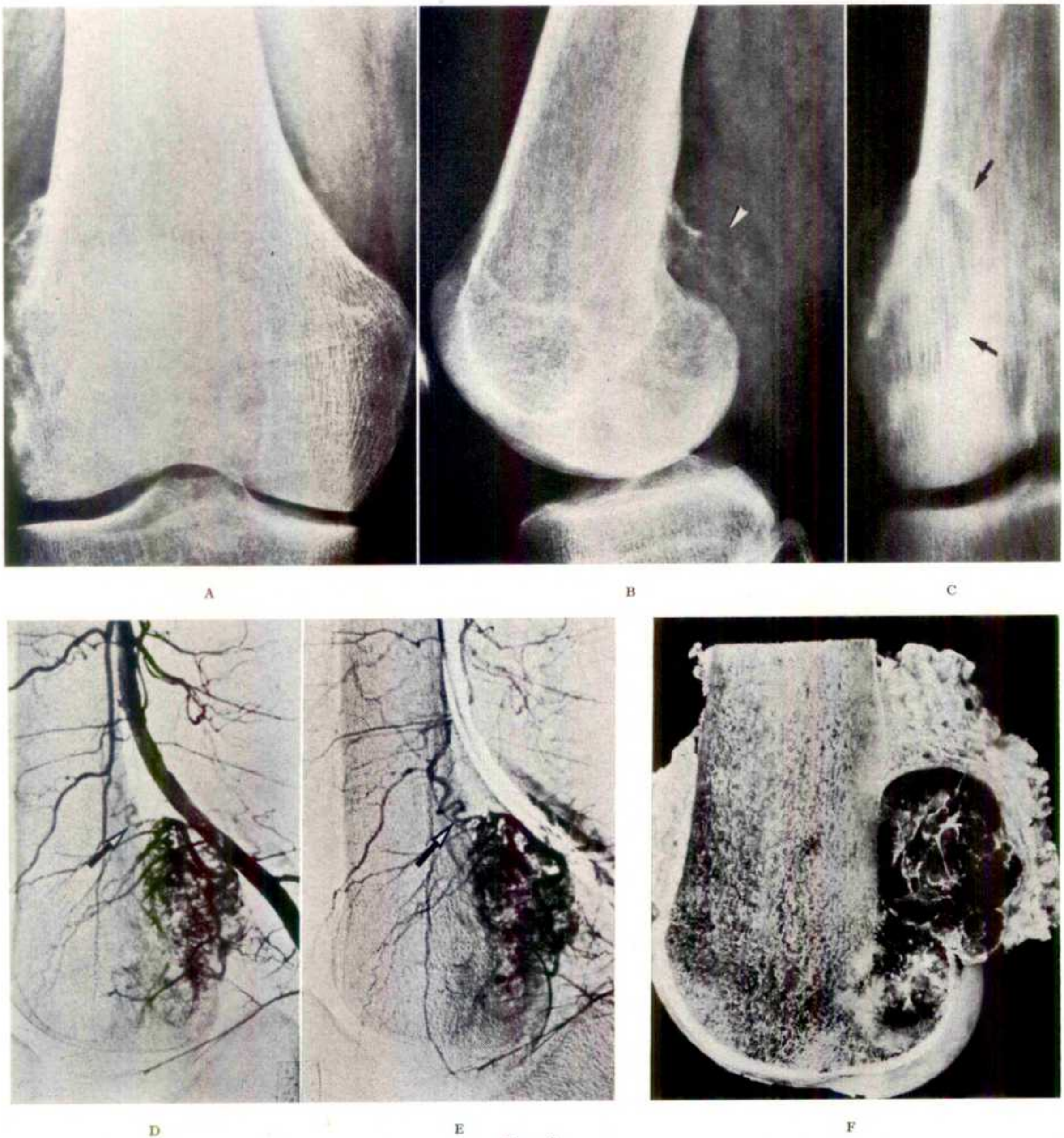

FIG. 3.
Male, 50 years. *Chondrosarcoma.* (A) Frontal, (B) lateral, (C) antero-posterior tomogram, (D) early, (E) late phase of angiogram, (F) operative specimen.

Plain film diagnosis: chondromyxoid fibroma (expanded, partially destroyed cortex (▶); sclerotic rim (➞)).
Angiographic diagnosis: malignant tumour (abundance of tumour vessels; focal arterio-venous shunting (➞).

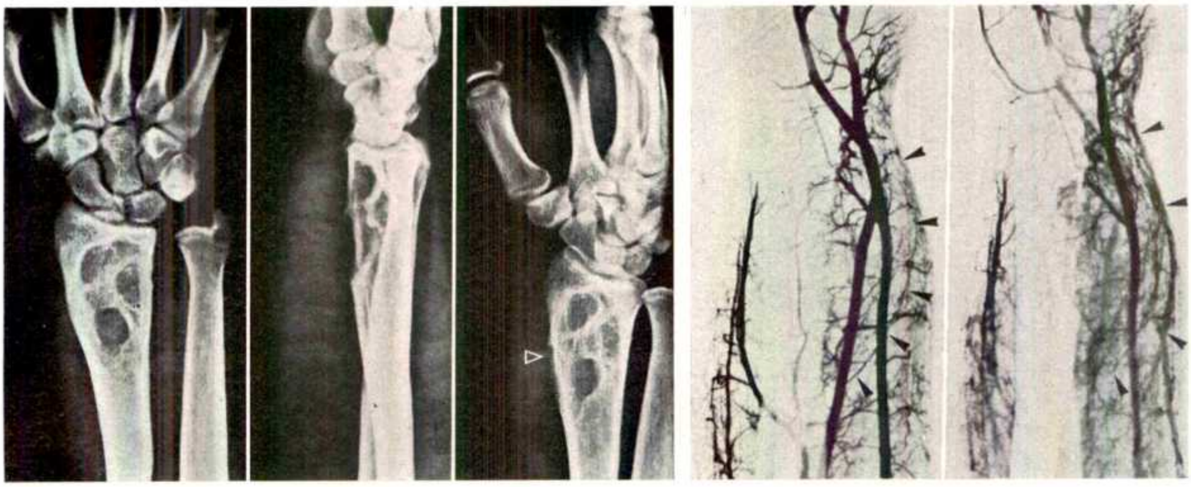

FIG. 4.

Male, 20 years. *Fibroma.* Plain film: primarily benign tumour with malignant degeneration (interrupted periosteal reaction (▷)). Angiogram (lateral view): benign tumour (displacement of vessels only (▶)).

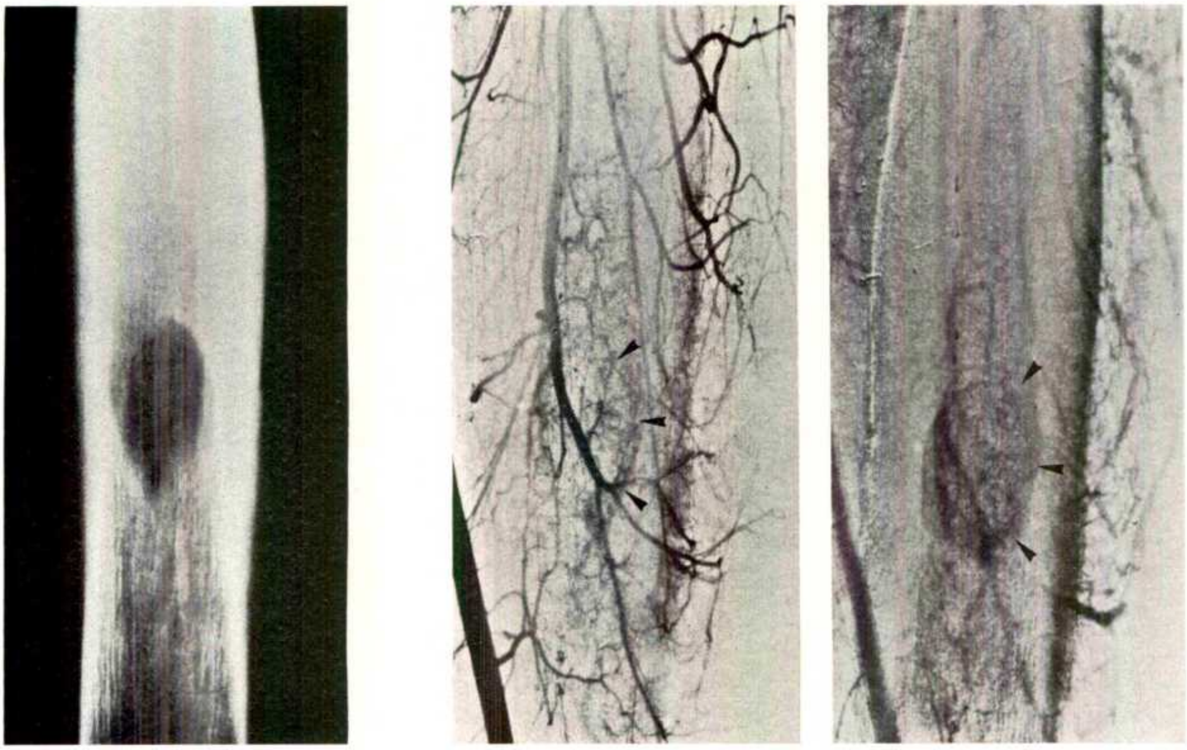

FIG. 5.

Male, 28 years. *Osteomyelitis.* Hypervascularity along the cortex and within the cavitary lesion of the medulla (▶), but no tumour vessels.

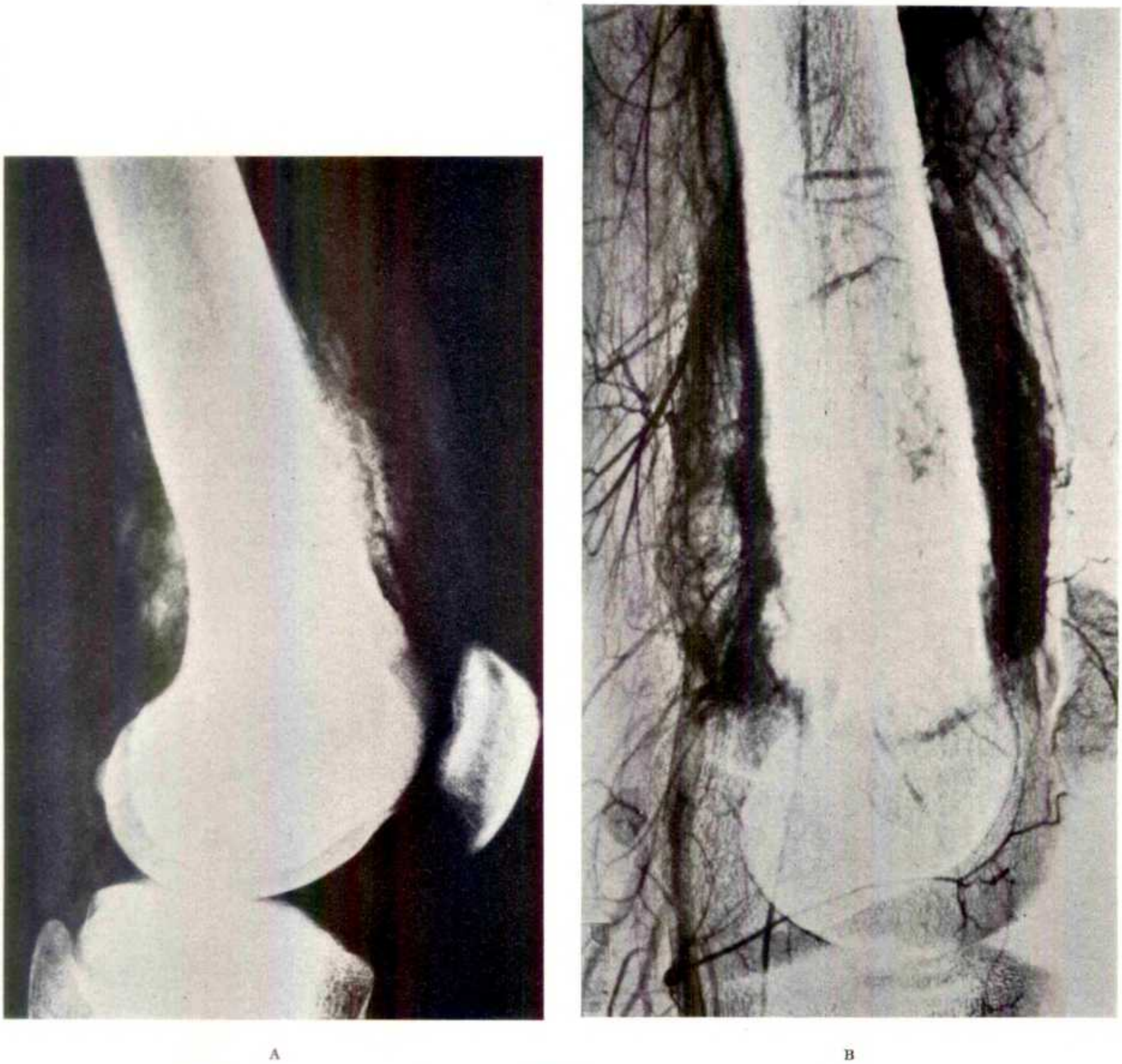

FIG. 6.

Male, 22 years. *Osteogenic sarcoma*. Better definition of tumour extent by angiography.

giant cell tumour and chondrosarcoma by one-fifth. Certain sarcomas, such as chondro- and fibro sarcomas, were at times only partially vascularized angiographically and presented, therefore, quite indistinct borders (Fig. 7).

3. *Prediction of histologic type*

The attempt to deduce from the angioarchitecture of a tumour characteristic vascular patterns, which could serve as predictor variables regarding histologic type, was generally unsuccessful in our material. There was, for instance, no difference in the appearance of tumour vessels between osteogenic sarcoma, Ewing's sarcoma and chondrosarcoma. The only exception to this observation was osteoid-osteoma, where a dense accumulation of contrast medium within the nidus during the capillary phase of the arteriogram is typical for this type of lesion (Fig. 8).

DISCUSSION

The above data indicate that arteriography has a definite place in the diagnosis and management of

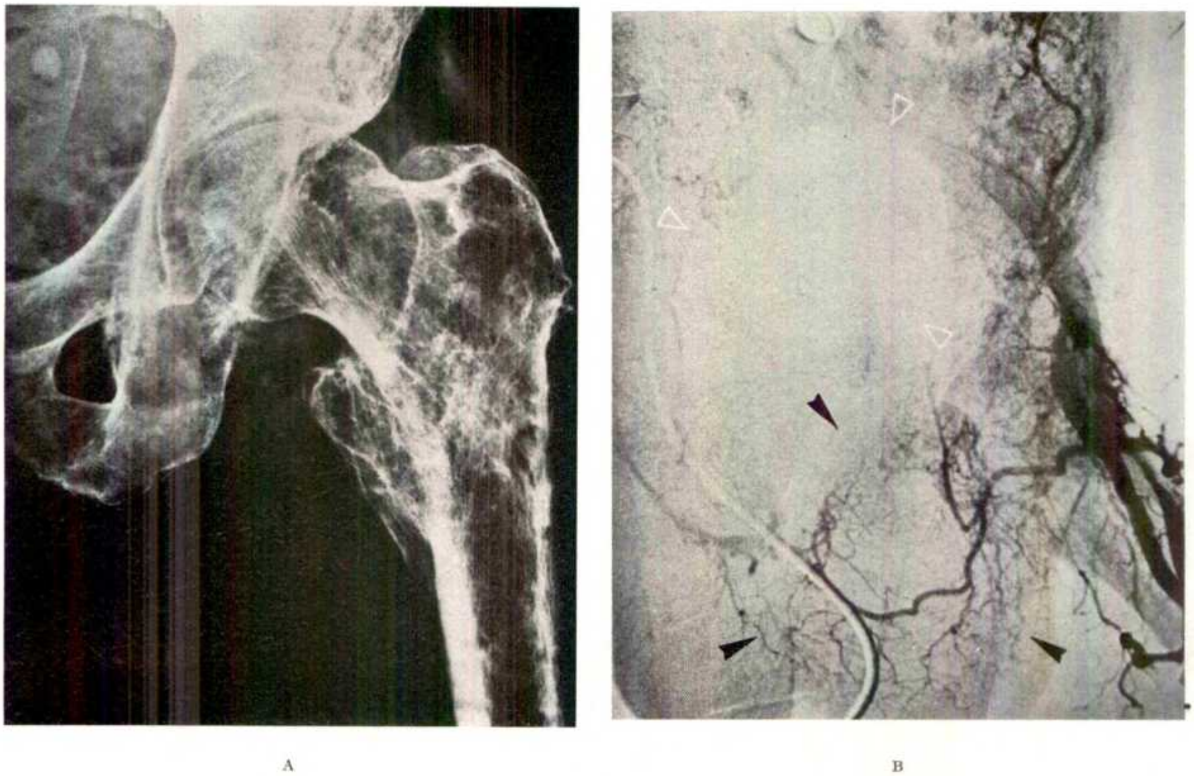

Fig. 7.

Male, 52 years. *Chondrosarcoma* (pelvis and proximal thigh). Tumour only partially vascularized (▶), whereas other areas remained avascular (▷).

bone tumours. This is particularly reflected by the increasing frequency with which we have been using this method over the past eight years. Above all, there has always been much debate about whether arteriography is apt to yield increased information over standard radiography in differentiating malignant from benign neoplasms, as well as from inflammatory lesions (Feldmann *et al.*, 1975; Halpern and Freiberger, 1970; Herzberg and Schreiber, 1971; Viamonte *et al.*, 1973; Yaghmai *et al.*, 1971).

From our results it can be concluded that arteriography, in addition to standard radiography, increases diagnostic accuracy in predicting benignity or malignancy by approximately 20 per cent. The most important finding, on which this differentiation is based is the presence or lack of tumour vessels (Billing and Lindgren, 1944; Herzberg and Schreiber, 1971); Lindgren, 1945; Strickland, 1959; Wenz *et al.*, 1971). Histologically, these tumour vessels appear as primitive vascular channels often consisting of only an endothelial layer surrounded by a connective tissue sheath, which maintain their thin walls even after they have grown to a larger size (Billing and Lindgren, 1944). This explains their irregular calibre as well as associated aneurysmal dilatations, characteristically seen on the arteriogram (Fig. 1). The decisive importance of demonstrating angiographically these irregular shaped tumour vessels is stressed by the close correlation between the tumour parenchyma and its vascular structures regarding the degree of differentiation (Billing and Lindgren, 1944; Dibbelt, 1914; Lindgren, 1945). In none of our benign tumours or inflammatory lesions were there any such tumour vessels discernible. In fact, most of the benign neoplasms of our series were strikingly hypovascular, characterized by vascular displacement rather than new vessel formation (Fig. 4). But it must also be kept in mind that absence of tumour vessels, or even hypo- or avascularity, does not rule out malignancy completely (Viamonte *et al.*, 1973). It has repeatedly been observed that centrally located and well vascularized bone tumours are not demonstrated arteriographically until the tumour has broken

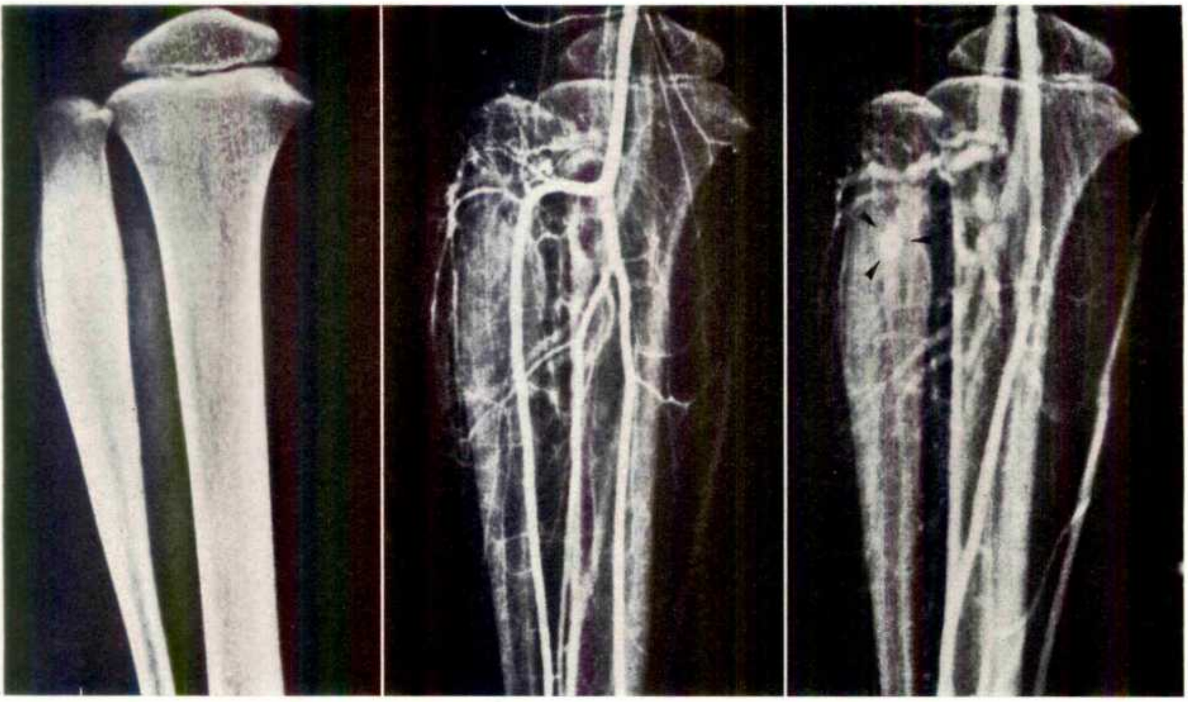

FIG. 8.

Male, 9 years. *Osteoid-Osteoma*. Hypervascularity with dense accumulation of contrast medium within the nidus (▶)

through the cortex. Some authors have, therefore, attempted to investigate bone tumours by direct intraosseous angiography (Klümper and Weller, 1970; Ratti, 1959). Furthermore, avascular areas might be due to either tumour necrosis or structural inhomogeneity (Fig. 7). It is well known to pathologists that bone tumours can be composed of more and less differentiated parts, as well as of quite different components (*e.g.*, osteogenic sarcoma with chondroblastic, osteoblastic and fibroblastic elements), which may markedly differ with regard to blood supply (Johnson, personal communication). It has, indeed, been shown by microangiographic studies that the most vascularized areas within a particular tumour correspond with its most malignant component (Lagergren *et al.*, 1958; 1961a; 1961b). This seems logical, since blood supply is essential for every living tissue, increased functional demand thus being met by the formation of new capillaries (Lindgren, 1945). Biopsy should preferably be taken, therefore, from hypervascular portions (Viamonte *et al.*, 1973). Increased vascularity, however, especially accumulation of contrast medium during the capillary phase of the arteriogram, is not a specific sign of malignancy. It might well be present in benign tumours (such as aneurysmal bone cyst and osteoid osteoma) and is an almost constant finding of inflammatory disease (Gronner, 1972; Härtel, 1971; Hutcheson *et al.*, 1972; Lagergren *et al.*, 1958; Lindbom *et al.*, 1960; 1961; Viamonte *et al.*, 1973). The angiographic differentiation between benign and malignant lesions is, therefore, mainly dependent upon the presence or absence of tumour vessels. This criterion has a decisive significance in cases where the differential diagnosis is impossible on clinical grounds and by conventional radiography (Fig. 5). The identification of tumour vessels is primarily based upon the excellence of the examination technique, which is of fundamental importance for optimum film interpretation. Proper film quality is obtained by following three basic principles:

(1) The contrast medium must be injected as close as possible to the disease process. Selective catheter arteriography is, therefore, essential for appropriate opacification of the vascular bed.

(2) The disease process has to be investigated in at least two different projections (as is the rule in every radiological examination).

(3) Superimposition of bone and calcifications on vascular structures should be eliminated by using subtraction films (Probst, 1971; Rittmeyer and Freyschmidt, 1971). Magnification- as well as pharmacoangiography may also be helpful (Ekelund and Lunderquist, 1974; Hawkins and Hudson, 1974; Rockoff *et al.*, 1966).

In conclusion, arteriography is not a routine procedure in the diagnosis of all presumptive bone neoplasms. From our experience arteriography is unnecessary if the lesion is unequivocally benign on standard radiography. If the lesion is definitely malignant by standard techniques, arteriography might be performed for better delineation of tumour extent, which is of utmost importance if radiotherapy is applied. In the group of low-grade malignant bone neoplasms (such as giant cell tumour, chondromyxoid fibroma, certain chondromas, such as the one of pelvic location and parosteal osteogenic sarcoma) arteriography might be performed for tumour grading, by using the presence or absence of tumour vessels as a predictor variable for the degree of tumour aggressiveness. Grading in these type of tumours is quite often impossible histologically (even on open biopsy) and by conventional radiography (Mucchi *et al.*, 1966; Probst, 1971; Uehlinger, 1974). In cases where standard radiography is non-diagnostic, and if there is any doubt as to whether a lesion is benign or malignant, arteriography represents a most useful guide to establishing the diagnosis by helping to differentiate benign from malignant disease, by defining the extent of the lesion and by assisting in the selection of the best site for biopsy.

REFERENCES

Billing, L., and Lindgren, A. G. H., 1944. Die pathologisch-anatomische Unterlage der Geschwulstarteriographie. *Acta Radiologica*, *25*, 625–683.

Dibbelt, W., 1914. Ueber die Blutgefässe bei Tumoren. *Arbeiten über pathologische Anatomie*, *8*, 114–128.

Ekelund, L., and Lunderquist, A., 1974. Pharmacoangiography with Angiotensin. *Radiology*, *110*, 533–552.

Feldmann, F., Casarella, W. J., Dick, H. M., and Hollander, B. A., 1975. Selective intra-arterial embolization of bone tumors. *American Journal of Roentgenology*, *123*, 130–139.

Gronner, A. T., 1972. Muscle necrosis simulating a malignant tumor angiographically. *Radiology*, *103*, 309–310.

Halpern, M., and Freiberger R. H., 1970. Arteriography as a diagnostic procedure in bone disease. *Radiological Clinics of North America*, *8*, 277–288.

Härtel, M., 1971. Angiographische Befunde kindlicher Knochentumoren. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin*, *115*, 582–589.

Hawkins, I. F., and Hudson, T., 1974. Priscoline in bone and soft-tissue angiography. *Radiology*, *110*, 541–546.

Herzberg, D. L., and Schreiber, M. H., 1971. Angiography in mass lesions of the extremities. *American Journal of Roentgenology*, *111*, 541–546.

Hutcheson, J., Klatte, E. C., and Kremp, R., 1972. The angiographic appearance of myositis osificans circumscripta. *Radiology*, *102*, 57–58.

Johnson, L. G., 1974 (personal communication).

Klümper, A., and Weller, S., 1970. The possibilities of peripheral arteriography and the significance of intraosseous angiography in the indication for operative treatment of bone tumors. In G. Chapchal *Operative treatment of bone tumors* (Georg Thieme, Stuttgart).

Lagergren, C., Lindbom, A., and Söderberg, G., 1958. Hypervascularization in chronic inflammation demonstrated by angiography. *Acta Radiologica*, *49*, 441–452.
1960. Vascularization of fibromatous and fibrosarcomatous tumors. *Acta Radiologica*, *53*, 1–16.
1961a. The blood vessels of osteogenic sarcomas. *Acta Radiologica*, *55*, 161–176.
1961b. The blood vessels of chondrosarcomas. *Acta Radiologica*, *55*, 321–328.

Lindbom, A., Lindvall, N., Söderberg, G., and Spjut, H. J., 1960. Angiography in osteoid-osteoma. *Acta Radiologica*, *54*, 327–334.

Lindbom, A., Söderberg, G., Spjut, H. J., and Sunquist, O., 1961. Angiography of aneurysmal bone cyst. *Acta Radiologica*, *55*, 12–17.

Lindgren, A. G. H., 1945. The vascular supply of tumors with special reference to the capillary angioarchitecture. *Acta Radiologica et Microbiologica Scandinavica*, *22*, 493–522.

Lodwick, G. S., 1971. *The bones and joints. An atlas of tumor radiology* (Year Book Medical Publishers, Chicago).

Mucchi, L., Goidanich, J. F., and Zanoli, S., 1966. *Angiographie in der Knochenpathologie* (Georg Thieme, Stuttgart).

Probst, F. P., 1971. Angiography in juxtacortical osteosarcomas. *Acta Radiologica* (*Diagnosis*), *11*, 49–56.

Ratti, A., 1959. L'arteriografia e l'osteomedullografia nella diagnosi dei tumori delle ossa. *Radiologica Clinica et Biologica*, *28*, 263–275.

Rittmeyer, K., and Freyschmidt, J., 1971. Der Wert des Subtraktionsverfahrens bei angiographischen Untersuchungen von Skelett-Tumoren. *Fortschritte auf dem Gebiete der Röntgenstrahlen under der Nuklearmedizin*, *114*, 656–662.

Rockoff, S. D., Doppman, J., Block, J. B., and Ketcham, A., 1966. Variable response of tumor vessels to intraarterial Epinephrine. *Investigative Radiology*, *3*, 205–213.

Strickland, B., 1959. Value of arteriography in diagnosis of bone tumours. *British Journal of Radiology*, *32*, 705–713.

Uehlinger, E., 1974. Pathologische Anatomie der Knochengeschwülste. *Chirurg*, *45*, 62–70.

Wenz, W., van Kaick, G., and Wegener, K., 1971. Kritisches zur angiographischen "Tumoranfärbung". *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin*, *115*, 180–185.

Viamonte, M., Roen, S., and Le Page, J., 1973. Non-specificity of abnormal vascularity in the angiographic diagnosis of malignant neoplasms. *Radiology*, *106*, 59–63.

Yaghmai, J., Shamsa, A. Z., Shariat, S., and Afshari, R., 1971. Value of arteriography in the diagnosis of benign and malignant bone lesions. *Cancer*, *27*, 1134–1147.

1976, *British Journal of Radiology*, *49*, 416–419

The multiple sclerotic osteogenic sarcoma of early childhood

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(*Submitted June, 1974 and in revised form November, 1975*)

ABSTRACT

Two cases of sclerosing osteogenic sarcoma that occurred in early childhood are reported. They and the similar cases reviewed are unusual in their development at an unusually early age, their multicentric presentation and their densely sclerotic nature. These are uncommon manifestations of osteogenic sarcoma and are considered due to proliferative metastatic osteoid formation in areas of rapid bone growth.

The appearance of apparently simultaneous osteogenic sarcomas in multiple sites is an uncommon condition that has been termed sclerosing osteogenic sarcomatosis by Moseley and Bass (1956), Singleton *et al.* (1962), Morse *et al.* (1962). These authors and others, Silverman (1936), Jaffe (1958) and Lichtenstein (1959) considered the possibility that osteogenic sarcomas could be multicentric in origin.

A feature of this type of osteogenic sarcoma is that it presents with densely sclerotic lesions at the metaphyseal ends of the long bones and with apparently simultaneous involvement of ribs, clavicles, numerous round and flat bones, the vertebrae and several epiphyses. The process may remain confined to the bone or break through the cortex, and soft tissue calcification is not infrequent.

Fifty-seven proven osteogenic sarcomas have been investigated at the Groote Schuur Hospital Tumour Clinic in the last ten years (1965–1974). The two youngest were cases of this type. We have therefore named them the sclerotic osteogenic sarcoma of early childhood. They are reported because there is a distinct possibility that they represent rapidly appearing metastases which are peculiar to this densely sclerotic osteosarcoma, rather than a multicentric condition as favoured by the previously mentioned authors.

CASE REPORTS

Case 1

A ten-year-old coloured male presented with a painful swelling of the distal right femur of four months' duration. There was a fusiform swelling involving the lower third of the right femur, and the right inguinal glands were enlarged and stony hard. The relevant blood examination figures were: haemoglobin 14·5 g per cent, white cell count 10,600 per ml., and alkaline phosphatase in excess of 57 Bodansky units per 100 ml. (Normal range 5–15 units in children.)

The radiological examination revealed a large sclerotic lesion in the distal two-thirds of the right femur which had involved the surrounding soft tissues and opacified the right inguinal glands. Sclerotic deposits were also present in the proximal femur of the same side (Fig. 1), proximal and distal metaphysis and epiphyses of the opposite femur and both tibiae, both scapulae, the proximal right and left humeri (Fig. 2), the 5th lumbar vertebra, and the sacrum and pelvis (Fig. 3). An initial chest radiograph appeared clear of lung metastasis but sclerotic deposits were present in the 11th and 12th dorsal vertebrae. An excision biopsy of the right inguinal lymph gland was performed. Histology showed total replacement of the node by metastatic osteosclerotic osteogenic sarcoma (Fig. 4).

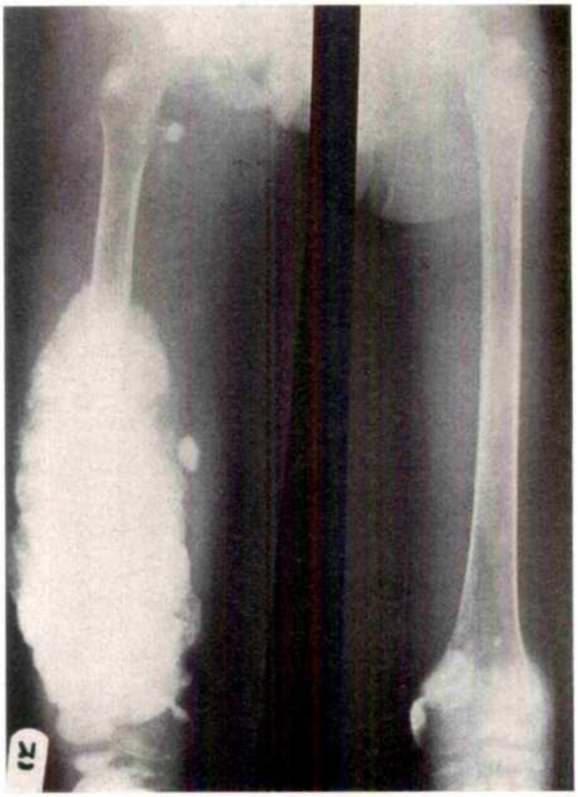

FIG. 1.

The large primary sclerotic osteogenic sarcoma of the right lower femur with metastases to the right inguinal lymph nodes, proximal right and left femora and both proximal tibiae. Note epiphyseal involvement.

The patient received radiotherapy to the lumbar spine and right femur in divided doses in conjunction with oral cytotoxics, Endoxan (25 mg) and Methotrexate (1·25 mg) were given daily. The mass in the lower right femur responded to therapy and the pain diminished. A chest radiograph two months after admission revealed metastatic deposits in both lungs with areas of ossification within them (Fig. 5). The patient developed chicken pox and cytotoxics were stopped for two weeks; thereafter the Endoxan and Methotrexate were discontinued and intravenous Vincristine (1 gm daily) was given. The patient died one month later.

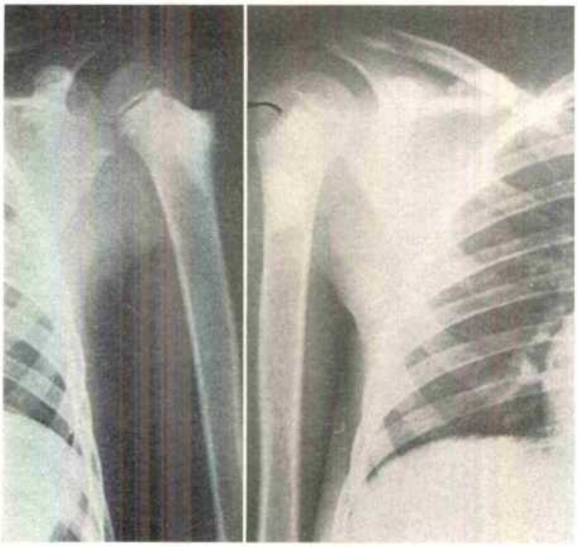

FIG. 2.
Sclerotic metastases shown in both proximal humeri and scapulae.

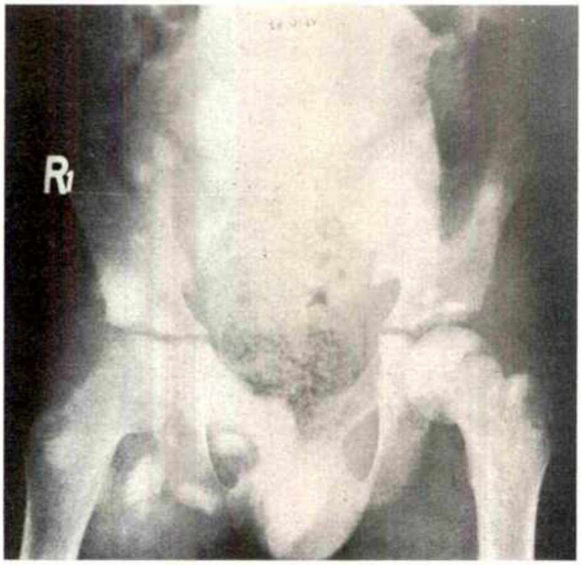

FIG. 3.
Sclerotic metastases to L.5, sacrum and pelvis and right inguinal lymph nodes.

The significant autopsy findings were: the tumour of the right femur involved the distal two-thirds of the bone and had invaded both epicondyles. Its transverse diameter was 9 cm and its cut surface was bony hard and yellow in colour. Small tumour nodules were present in the remainder of the medullary cavity. Similar tumour nodules were found in the inner table of the skull, both scapulae, the proximal ends of both humeri, the manubrium sterni, the vertebral column and the inner surface of the ribs. Both lungs contained metastases, the largest nodules being 7 cm in diameter and further metastases were found in the mediastinal and hilar lymph nodes, the visceral and parietal pleura and the right side of the crebellum. Microscopically, these metastases had the same appearance as the primary tumour with abundant osteoid and extensive calcification separating the malignant cells (Fig. 6).

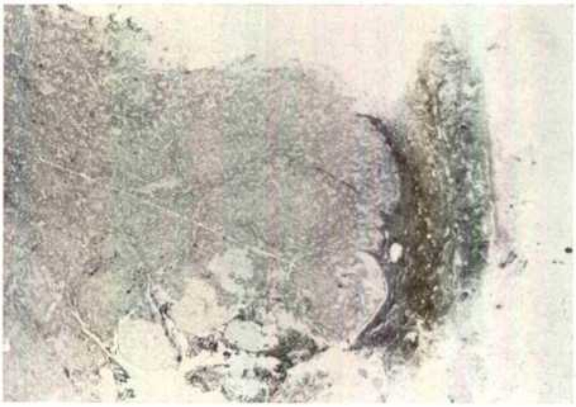

FIG. 4.
Section of the lymph node biopsy shows replacement of the node by osteogenic sarcoma. (H & E × 22).

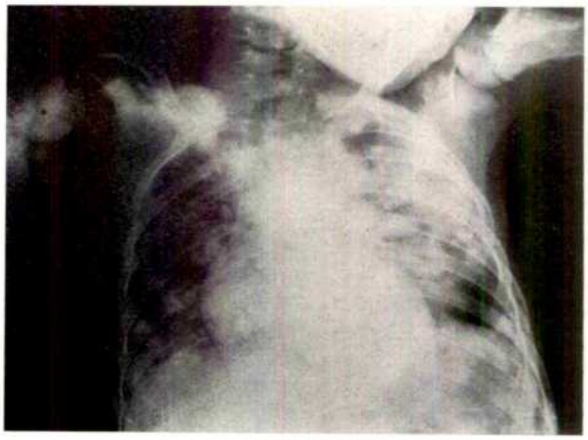

FIG. 5.
Ossifying pulmonary metastases and sclerosing osteogenic sarcoma metastases to the scapulae and proximal humeri are shown.

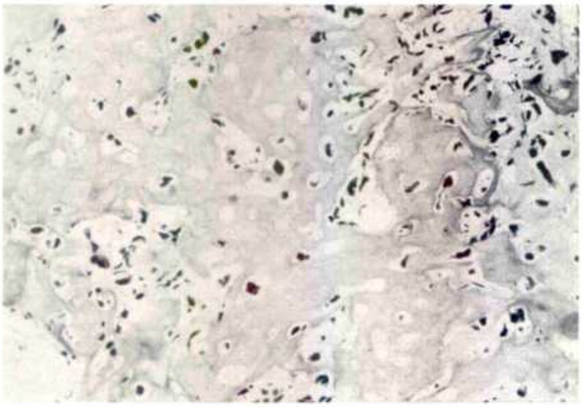

FIG. 6.

Section of lung metastasis showing sclerotic osteogenic sarcoma. (H & E ×320).

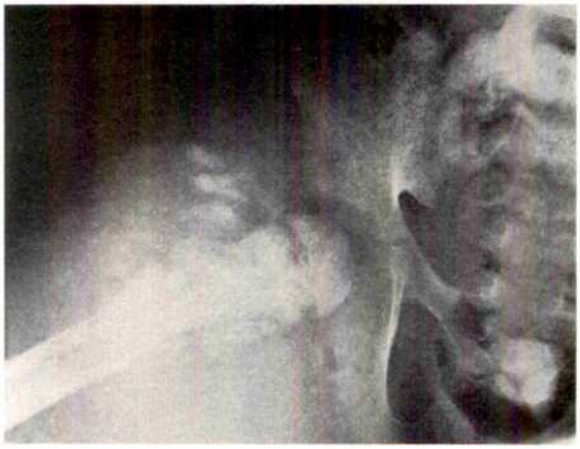

FIG. 7.

The large sclerotic primary sarcoma involving the proximal right femur with L.5 and sacral metastases are seen.

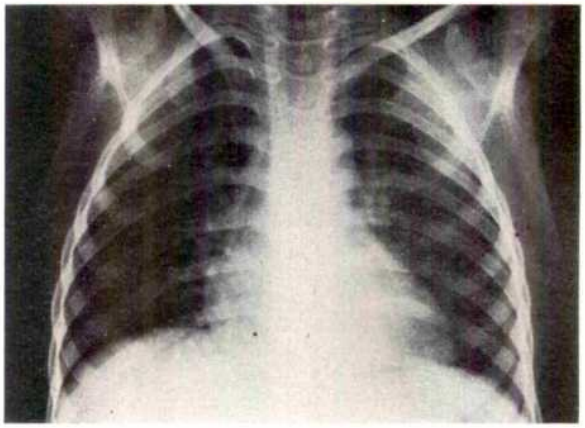

FIG. 8.

The chest radiograph is clear of pulmonary metastases.

Case 2

A seven-year-old coloured boy presented with pain and swelling of the right hip following an injury five months previously. The right thigh in the region of the hip was grossly swollen, firm and indurated. The relevant blood examination figures were: haemoglobin 12·6 gm per cent, white cell count 11,300 per ml., and alkaline phosphatase 486 Bodanski units per 100 ml. A radiograph of the right femur and pelvis (Fig. 7) revealed a sclerosing lesion of the proximal femur invading the soft tissues. Sclerotic lesions were also present in L.5, the third part of the sacrum and the twelfth thoracic vertebral body, and the angle of the eleventh left rib. The chest radiograph appeared normal (Fig. 8).

A needle biopsy of the right femur confirmed the diagnosis of an osteogenic sarcoma (Fig. 9A). The patient died suddenly four days later and significant autopsy findings were: Section of the right femur showed extensive involvement by a tumour which appeared cartilaginous in many areas (Fig. 9B). The tumour extended into the soft tissues laterally and also superiorly beneath the inguinal ligament to the level of the common iliac vessels where it abutted on the sacrum. A large mass was also present in the retroperitoneal tissues overlying the twelfth thoracic vertebral body. Multiple calcified pulmonary nodules measuring 0·5 to 2·0 cms were present in the lungs. Focal areas of infarction were present and both left and right pulmonary artery branches contained tumour embolism with a large embolus occluding the left main pulmonary artery. The histology of the primary lesion and the pulmonary metastases showed areas of osteosarcoma with osteoid formation directly from the sarcomatous cells, but there were in addition many areas which consisted of poorly differentiated chondrosarcomatous elements.

DISCUSSION

Although they did not draw attention to the sclerotic nature of the lesions, Halpert *et al.* (1949) described a seven-year-old girl with a sclerotic osteogenic sarcoma in her right knee with advanced bony sclerotic deposits and pulmonary involvement. The case described by Moseley and Bass (1955) was a five-year-old girl who also showed multiple sclerotic bone lesions with the most advanced one in the right tibia. The lungs though initially clear, were not apparently followed up. We have not access to the literature they quoted of a similar case of an eight-year-old Argentinian girl. The two cases of multiple lesions described by Singleton *et al.* (1956) were a six-year-old girl with a comparatively extensive lesion in her lower right femur and an initially clear chest radiograph, and a five-year-old boy with the predominant lesion in his upper left femur. This child had terminal ossified lung lesions. The six-year-old girl described by Morse *et al.* (1956) had the most advanced lesion in her upper left humerus and her chest radiograph showed calcified lung lesions which terminally became confluent.

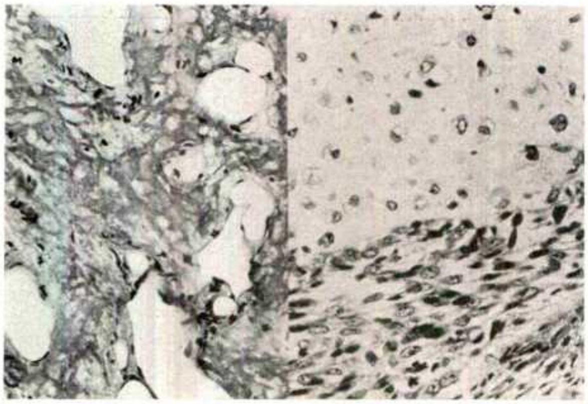

Fig. 9.

(A) Section of the needle biopsy of the primary tumour showing tumour osteoid. (H & E × 320).

(B) Section of the primary tumour at autopsy, showing undifferentiated sarcoma together with chondrosarcomatous element. (H & E × 320).

These reports and our two cases have the following unusual features which are grouped together for the first time:

1. *Age of patients*

All the cases quoted in the discussion occurred in children in the first decade of life, their ages ranging from five to eight years. This is an unusual predeliction for the lower end of the age spectrum of osteogenic sarcoma and may be one of the distinguishing features of this lesion.

2. *Multiplicity of lesions*

All these cases presented with multiple sclerotic bone lesions, and one of the limb lesions was always in a more advanced stage than the others. Although it is not uncommon for the radiologically visible bony metastasis to appear during the progression of an osteogenic sarcoma, a figure of 14 per cent being given by McKenna *et al.* (1966), it is uncommon for the first presentation to be in this manner.

The quoted authors considered a multicentric origin to be possible, but we consider metastasis from a primary in the limb to be a more likely explanation. Initially the chest radiographs may appear clear, but our Case 2 showed that this interpretation may be erroneous in the early stages. Metastases that seed in the lung may not show the same rapid growth as those that pass through into active bone growth or red marrow areas. Alternatively, the metastases may reach the bones via vertebral plexuses (Batson, 1957) or involve the lymphatics as was also demonstrated in our first case.

3. *Sclerotic nature of the deposits*

All the lesions were uniformly opaque and radiographically dense. They were bone-forming osteogenic sarcomas. When this occurs in the first decade of life it appears to be particularly malignant. An alternative explanation might be that, because the metastasis is sclerotic and because rapidly growing bone is a particularly suitable medium for prolific expansion, the metastasis is visualized at an early stage of the disease.

REFERENCES

Batson, O. V., 1957. Vertebral vein system. Caldwell Lecture 1956. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 78,* 195–212.

Halpert B., Russo, P. E., and Hackney V. C., 1949. Osteogenic sarcoma with multiple skeletal and visceral involvement. *Cancer, 2,* 789–792.

Jaffe H. 1958. *Tumours and Tumourous Conditions of Bones and Joints.* pp. 266 (Philadelphia, Lea and Febiger).

Lichtenstein, L., 1959. *Bone Tumours.* 2nd edn., pp. 206 (C. V. Mosby, St. Louis).

McKenna, R. J., Schwinn, C. P., Soong, K. Y., and Higinborthan, N. L., 1966. Sarcomata of the osteogenic series (osteosarcoma, fibrosarcoma, chondrosarcoma, parosteal osteogenic sarcoma and sarcoma arising in abornal bone). An analysis of 552 cases. *Journal of Bone and Joint Surgery, 48A, 1,* 1–26.

Moseley, J. E., and Bass, M. H., 1956. Sclerosing osteogenic sarcomatosis (a radiological entity). *Radiology, 66,* 41–45.

Silverman, G., 1936. Multiple osteogenic sarcoma. *Archives of Pathology, 21,* 88–95.

Morse, D., Reed, J. O., and Bernstein, J., 1962. Sclerosing osteogenic sarcoma. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 88,* 491–495.

Singleton, E. B., Rosenberg, H. S., Dodd, G. D., and Dolan, P. A., 1962. Sclerosing osteogenic sarcomatosis. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 88,* 483–490.

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1976, *British Journal of Radiology*, *49*, 420–424

Radiology of acalculous gall-bladder disease—a new sign

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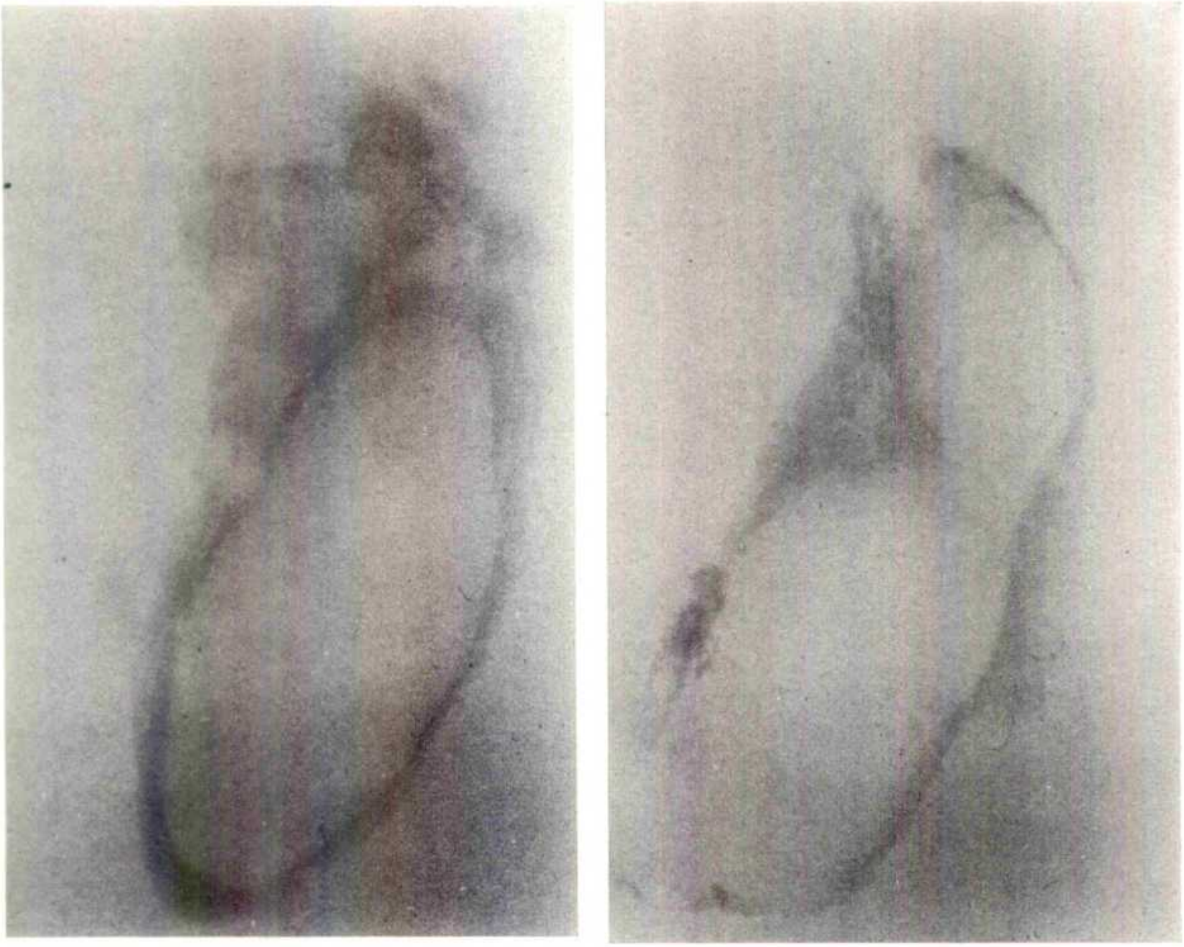
(*Received August, 1975*)

ABSTRACT

Radiography of excised gall-bladders, immersed in water, has shown that chronically infected gall-bladders frequently contain fat. This fat can be seen *in vivo*, and the frequency of the finding was assessed by reviewing 43 patients with acalculous gall-bladder disease. Other radiological signs in the cholecystograms were looked for retrospectively, and their incidence assessed. In 20 cases out of 40, no radiological abnormality was found.

> "In rare cases the thickened and inflamed wall of the gall-bladder may show an abundant deposit of fat, evenly distributed throughout, or placed irregularly in larger or smaller masses."
>
> Moynihan (1905) writing on chronic cholecystitis

It has long been recognized that gall-bladder abnormalities may occur in the absence of stone formation. These abnormalities include chronic infection, adenomyomatosis and cholesterolosis, and were grouped under the term cholecystoses by Jutras



A

B

FIG. 1.

(A and B) Radiographs of excised gall-bladders immersed in water and radiographed. Note the fat, varying in thickness. Pathological evidence of chronic cholecystitis was found.

(1960). Many of these patients have symptoms indistinguishable from gall-stone disease (Anderson *et al.*, 1971). Cholecystectomy leads to relief of symptoms in a large majority of these patients (Gunn *et al.*, 1973; Glenn and Mannix, 1956).

Recognized radiological signs of chronic mural disease of the gall-bladder are:

(1) Cholesterolosis. On cholecystography, cholesterol polyps are seen as filling defects in the gall-bladder, distinguished from non-opaque stones because of their unchanging position.

(2) Mucosal hypertrophy. Gland hyperplasia initially causes blurring of the outline of the gall-bladder, often involving only a segment of the border (cholecystitis glandularis proliferans). Later the glands erode into the muscle layers (adenomyomatosis).

The mucosal thickening can cause septum formation, and give the gall-bladder an abnormal shape (Colquhoun, 1961).

(3) Failure of opacification on oral cholecystography.

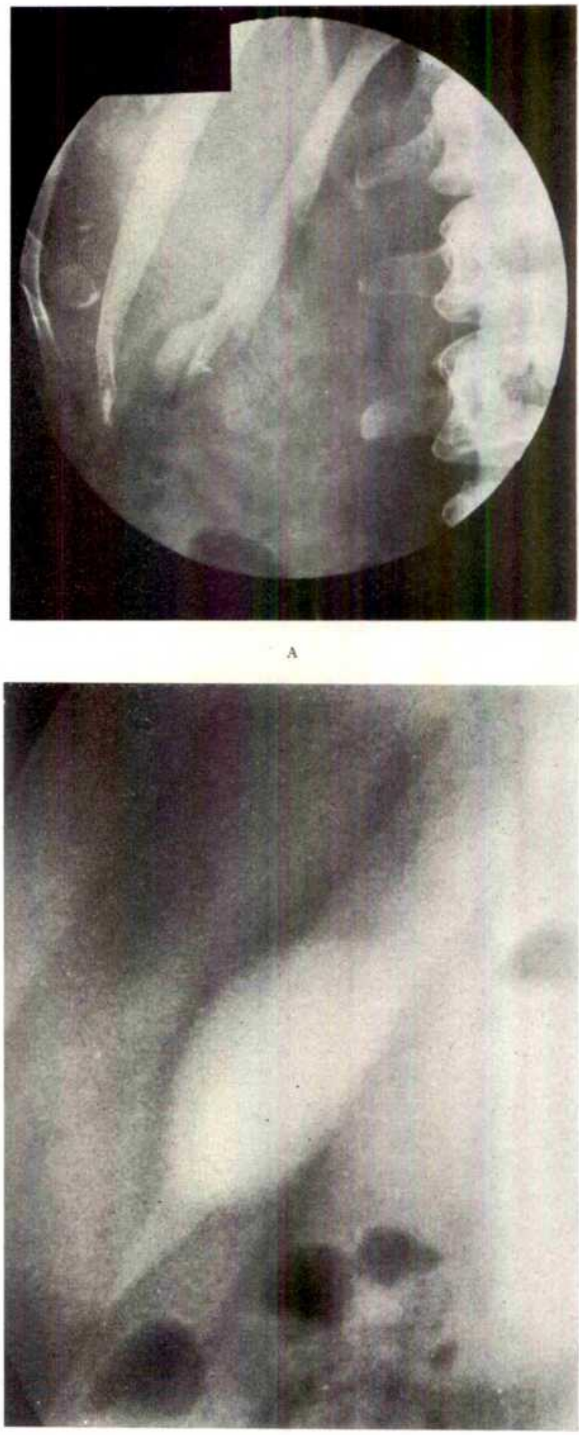
Other rarer signs which we did not see during this review are:

(1) calcified gall-bladder wall;
(2) limey bile;
(3) intramural bullae;
(4) tumours of the gall-bladder.

This review determines the incidence of these signs in acalculous gall-bladder disease and assesses an undescribed sign of gall-bladder disease by identification of fat in the wall.

We have confirmed Moynihan's observation that fat is found in the wall of gall-bladders in chronic cholecystitis. If an excised gall-bladder is immersed in water and radiographed, the resultant film clearly demonstrates mural fat if it is present. A normal gall-bladder contains little fat (Ham, 1974) and is invisible on radiography in water. It is difficult to get provenly normal gall-bladders. Normal gall-bladders are not removed at cholecystectomy, and at death autolysis rapidly destroys histological proof of normality. A group of 20 gall-bladders, macroscopically normal on excision at post-mortem, were radiographed under water. Fat was seen only once, in a gall-bladder where it was less than 1 mm thick and evenly distributed. Conversely we found fat frequently on radiography under water in the wall of abnormal gall-bladders in the excised specimens (Fig. 1), and also on abdominal radiography.

This fat, being "inflammatory fat", is less translucent than pure fat and a low kilovoltage is necessary for its demonstration in life (Fig. 2). Photographic effects can produce apparent dark rings around images (Mackie, 1917) and so 4 mm was set


A

B

FIG. 2.

(A) A gall-bladder at cholecystography. Note the negative density of fat especially on the right border—this is an inflamed gall-bladder, confirmed at surgery.
(B) A similar case. Note the "halo" of fat.

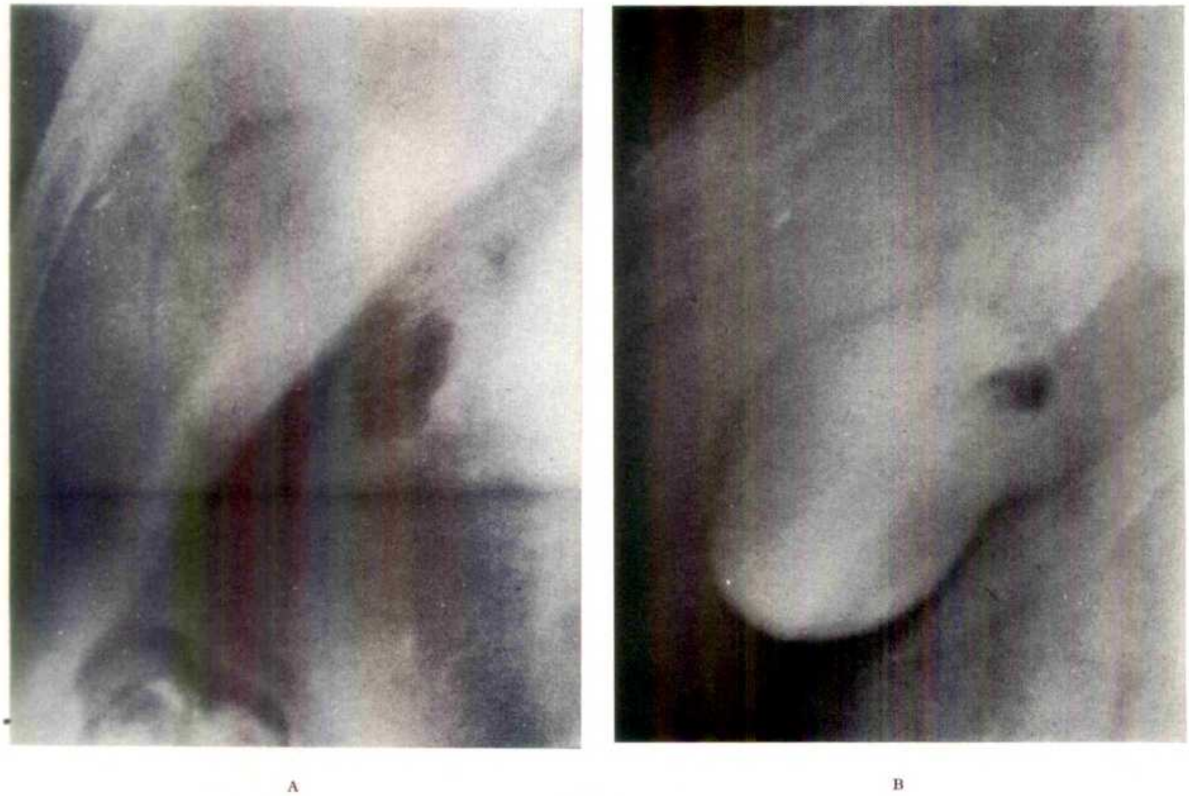


Fig. 3.

(A and B) A plain film shows a fine crescentic shadow, which on cholecystography is seen to be the gall-bladder wall.

as the minimum thickness to be present to allow unequivocal acceptance of the presence of a "fat sign". The thickness of the perivesical fat is often irregular and can be more than 10 mm in thickness. Confusing shadows in the gall-bladder area make it virtually impossible to be dogmatic about the presence of a "fat sign" without a cholecystogram (Fig. 3) or gall-stones (Fig. 4) to localize the gall-bladder, but retrospective review of the plain films after cholecystography often shows the fat line is present. Cholelithiasis is frequently present without fat in the wall, and conversely fat may be present without cholelithiasis. Fat of greater thickness than 4 mm is present only in a small proportion of cases.

A review was made of 64 cases of acalculous gall-bladder disease. Patients were admitted to the series with these criteria:

(1) They had abdominal pain. Most also had other symptoms, *e.g.* fat intolerance, nausea, vomiting or flatulence.

(2) At laparotomy no lesion was found other than gall-bladder disease.

(3) The gall-bladder disease was confirmed at pathological study.

(4) No gall-stones were found at cholecystectomy.

Of these 64, 58 were relieved of their symptoms on follow-up after an interval of two to eight years. A fuller review of the clinical aspects of these patients is in preparation.

Of these 64 patients, the cholecystograms carried out prior to surgery were available for 49 patients. A retrospective review was made of these, looking for radiological signs of disease.

(1) No opacification. Our patients took six capsules of sodium iopodate, 0·5 g (Biloptin) at 21.00 hours, and were radiographed the following morning. If the gall-bladder was not seen a further 12 capsules were given the same evening. If no gall bladder was seen next day it was accepted as not opacifying.

(2) Poor function. If the gall-bladder was seen but the density was no better than other soft tissue shadows the function was said to be poor.

(3) Cholesterol polyps. Negative shadows were seen

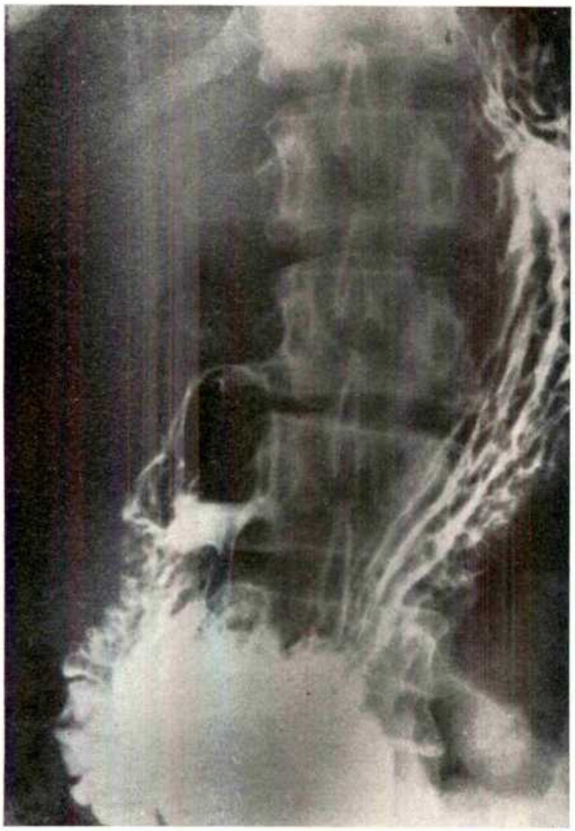


FIG. 4.

The calcification above the duodenal cap is confirmed as a gall-stone in the gall-bladder because of the "halo" of mural fat.

TABLE I

INCIDENCE OF RADIOLOGICAL SIGNS IN ACALCULOUS GALL-BLADDER DISEASE

43 patients	
No opacification	5
Poor function	6
Cholesterol polyp	1
Adenomyomatosis	1
Septum	2
Blurring of outline	1
Fat sign	6
Abnormal shape	1
No abnormality seen	20

in the lumen, unaltering in their position with postural change.

(4) Adenomyomatosis. Intra-mural diverticulum formation, as illustrated by Colquhoun (1961).

(5) Blurring of outline. This is a difficult and subjective assessment. Respiratory and other movement may blur the gall-bladder outline, but occasionally a crenation or "fuzziness" of the outline can be identified, often involving part of the outline only. The cases regarded as positive showed a fine crenation.

(6) "Fat sign". The negative density of perivesical fat of 4 mm or more in thickness at one point.

(7) Septum >4 mm. The mucosal proliferation makes a septum, again illustrated by Colquhoun.

(8) Abnormal shape of gall-bladder. Again this is a subjective sign. The mucosal hypertrophy gives an abnormal shape to the outline, in particular after a fatty meal when the gall-bladder may divide into locules of contrast. This sign was recorded as present when such loculation occurred.

(9) Gall-stones. These were seen in six patients at cholecystography, although no stones were found at cholecystectomy. These cases serve as a reminder that "acalculous gall-bladder disease" is a diagnosis made at a moment in time—in this series at the laparotomy. The diagnosis does not preclude stone formation earlier (or later) in the disease process.

These six cases are excluded from Table I, leaving 43 cases for the analysis of the frequency of occurrence of these signs.

CONCLUSIONS

Radiological diagnosis of acalculous gall-bladder disease was possible in only about half the cases. Many patients had normal cholecystograms. In particular it is disappointing to note the low incidence of conventional signs of mural disease—adenomyomatosis and septum formation. The "fat sign" on occasion is helpful and was the only sign present in six cases.

A normal cholecystogram does not exclude gall-bladder disease.

As Fotopoulos and Crompton (1964) have stressed, the finding of a diseased gall-bladder on radiology is not of itself an indication for surgery.

ACKNOWLEDGMENT

We are grateful to the surgeons who provided excised gall-bladders for radiography, particularly Mr. H. B. Torrence.

REFERENCES

ANDERSON, A., BERGDAHL, L., and BOQUIST, L., 1971. Acalculous cholecystitis. *American Journal of Surgery*, *122*, 3–6.

COLQUHOUN, J., 1961. Adenomyomatosis of the gall-bladder (intramural diverticulosis). *British Journal of Radiology*, *34*, 101–112.

FOTOPOULOS, J. P., and CROMPTON, A. R., 1964. Adenomyomatosis of the gall-bladder. *Medical Clinics of North America*, *48*, 9–36.

GLENN, F., and MANNIX, H., 1956. The acalculous gall-bladder. *Annals of Surgery*, *144*, 670–678.

GUNN, A., KEDDIE, N. C., and FOX, H., 1973. Acalculous gall-bladder disease. *British Journal of Surgery*, *58*, 213–215.

HAM, A. W., 1974. *Histology*, p. 711 (Lippicott, Philadelphia).

JUTRAS, J. A., 1960. Intramural lesions of the gall-bladder. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *83*, 796–827.

MACKIE, A., 1917. Halation, the Mackie effect. *British Journal of Photography*, *64*, 11–12.

MOYNIHAN, B. G. A., 1905. *Gall-stones and their surgical treatment*, p. 67 (Saunders, London).

Book reviews

N.C.R.P. Report No. 46—Alpha-Emitting Particles in Lungs, pp. 27, 1975 (N.C.R.P. Publications, Washington), $3.00.

In the recent past there has been some controversy in the non-technical press over the "hot particle" problem, that is the possibility that plutonium in aggregates is much more efficient in causing cancer than when more or less uniformly distributed in a tissue. This is clearly a practical problem of some importance when considering the safety standards for air-borne plutonium which in practice will always be in particulate, not molecular, form. The Medical Research Council report "The Toxicity of Plutonium" (February 1975, H.M.S.O.) considered this and other sources of uncertainty about the basic health standards for plutonium workers and concluded that the current I.C.R.P. standards are in need of little or no modification.

This N.C.R.P. Report No. 46, *Alpha-Emitting Particles in Lungs* (issued August 15,1975) is a much slighter document written specifically for U.S.A. readers. It stresses specifically that its conclusions are neither an endorsement nor a commentary on the absolute numerical adequacy of present N.C.R.P. standards for plutonium or other alpha-emitting radionuclides. The main positive conclusion is "that the current N.C.R.P. practice of averaging over the lung the absorbed dose from particulate alpha-emitting radionuclides is a defensible procedure when employed in conjunction with appropriate dose limits". Outsiders may well agree with this conclusion while wondering if the limited experimental information (pages 7–8) can justifiably be described as "the substantial body of experimental animal data available at the present time".

R. H. MOLE.

Metabolic Disorders of Bone. By C. R. Paterson, pp 284, 1974 (Blackwell Scientific Publications), £8·25.

This comparatively short book with 284 pages of text contains a well-balanced account of the subject of metabolic bone disease. It is as up to date as is necessary for its purpose. It is well written and easy to read. The layout of the text and figures is particularly pleasing. It can be warmly recommended as excellent background reading for the radiologist with an interest in bones.

F. H. DOYLE.

International Encylopaedia of Pharmacology and Therapeutics. Section 79: Sulphur-containing Radioprotective Agents. Edited by Z. M. Bacq, pp. 346, 1975 (Oxford—New York, Pergamon Press), $50.

During the fifties some thousands of compounds were tested in mammals for their radioprotective activity. This expansive enterprise evidently gained its support from a call for defensive measures against some of the peripheral effects of nuclear warfare, which threatened more then than now. As always, the urgent social need could only be addressed to existing knowledge gained under the impulse of academic interest. The agents treated here had held attention by deserving features: they were active in simple systems under conditions which permitted plausible interpretation of their radioprotective effects in chemical terms; because many were present in measurable concentrations within normal cells, it was conceived that they could modulate the registration of radiation damage in cells; and a link with the oxygen effect was suggested by a likely implication of these agents in oxidative mechanisms. This last feature made it probable that administration of this class of compounds would be associated with toxic effects. Such proved to be the case; there was found to be a close association between their radioprotective and toxic effects, and this book records a large part of the endeavour to disentangle them. It turns out that the content refers more to toxicology than to radiobiology. The nine chapters, by nine Belgian authors, describe the general pharmacology of these agents and their extensive effects on the various systems of mammals; although many compounds are included in the class, a high proportion of the studies were made using cysteamine. The description of metabolic effects occupies a quarter of the book. A chapter by Bacq discusses protection by thiols against poisoning by radiomimetic agents.

The subject may appear to have a historical flavour and to appeal to an esoteric interest. However, the interaction of toxicity and chemical modification of radiation effects is a continuing concern, even when the orientation of interest changes, as it has, from protectors to sensitizers. And there is often novelty and wisdom in the application of older knowledge to newer problems. The book has over 700 references and is well indexed; but, at 14 cents a page, it is very expensive.

H. B. HEWITT.

1976, *British Journal of Radiology*, *49*, 425–426

Ultrasonic diagnosis of choledochal cyst in pregnancy

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(*Received November, 1975 and in revised form, December, 1975*)

ABSTRACT

Two patients are reported with obstructive jaundice in pregnancy. In one of these ultrasonic scanning confirmed a diagnosis of choledochal cyst, and in the other made this diagnosis.

Ultrasonic scanning is suggested as the preliminary radiological examination for obstructive jaundice in pregnancy. Any patient with a clinical diagnosis of choledochal cyst should have an ultrasonic scan.

Choledochal cysts are an uncommon cause of obstructive jaundice, but there is a tendency for them to present in pregnancy (Chesterman, 1944; Fleming, 1947). We present two cases in whom ultrasonic scanning proved valuable.

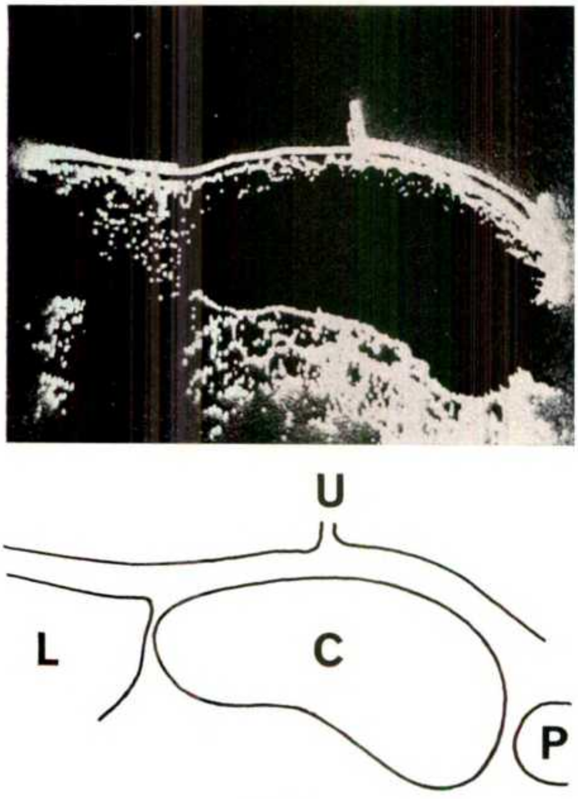

FIG. 1.

Vertical section 5 cm to the right of the midline showing the very large cyst. L—liver; C—cyst; P—pregnant uterus; U—umbilicus.

CASE REPORTS

Case 1

A 24-year-old teacher who was three months' pregnant, presented with a tender swelling in the right hypochondrium, which had been present for five weeks. For three weeks she had been mildly icteric. There was no obvious medical history of note.

There was a large, soft, slightly tender mass in the right abdomen. Serum albumen was 3·6 g per 100 ml.; serum globulins—2·7 g per 100 ml.; total bilirubin—11·2 mg per 100 ml., 9·6 mg per 100 ml. being direct; serum alkaline phosphatase was 34 KA units per 100 ml.; SGOT—40

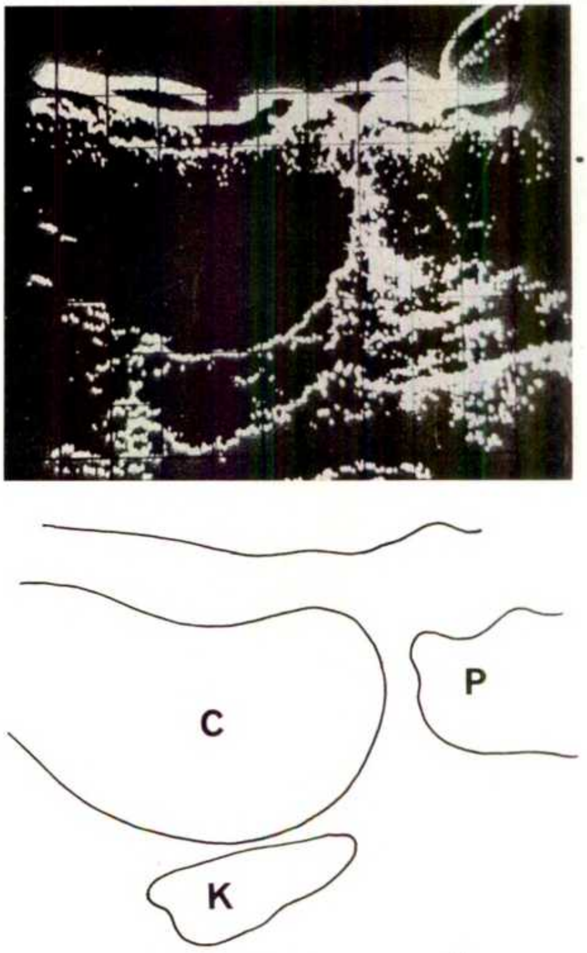

FIG. 2.

Vertical section 5 cm to the right of the midline. C—cyst; K—kidney; P—pregnant uterus.

IU/l. and SGPT—78 IU/l. An ultrasonic scan revealed a very large cyst in the right abdomen (Fig. 1).

At laparotomy a huge choledochal cyst was present. A choledochocyst-duodenostomy was carried out.

She made an excellent post-operative recovery. Her jaundice rapidly cleared and she went on to complete a normal pregnancy.

It is now over a year since the operation and she remains well.

Case 2

A 19-year-old sales assistant presented at the Manchester Royal Infirmary complaining of right hypochondrial pain of three weeks' duration, followed two weeks later by jaundice. She was five months' pregnant. An attack of acute pancreatitis one year previously was confirmed biochemically, but following this an oral cholecystogram was normal, as was the exocrine pancreatic function. Since then she had been subject to recurring attacks of colicky, right upper quadrant pain and had been slightly icteric on one previous occasion.

On examination she was mildly icteric and no definite mass was felt in the right hypochondrium. Serum albumen was 3·7 g per 100 ml.; total protein—7·0 g per 100 ml.; serum bilirubin—2·8 mg per 100 ml.; serum alkaline phosphatase—12·8 KA units per 100 ml.; SGOT—84 IU/l. and serum amylase—640 IU/l. An ultrasonic scan taken three days after admission revealed a large cyst below the liver (Fig. 2).

A diagnosis was made of a choledochal cyst.

At laparotomy the diagnosis was confirmed. A choledochocyst-duodenostomy was performed, the anastomosis being carried out at the junction of the first and second parts of the duodenum.

The patient made an excellent post-operative recovery and her pregnancy progressed uneventfully.

Comment

Since the initial description in 1724 by Vater (Lavenson, 1909) more than 400 cases (Alonso-Lej *et al.*, 1959) of choledochal cyst have been described. The majority are diagnosed in childhood and 80 per cent in females. They are commoner in Japanese (Lichtman, 1953). In pregnancy as the abdomen is distended by the enlarging uterus a cyst may become difficult to palpate, as in our second case.

Obstructive jaundice in pregnancy is most usually due to an intrahepatic cholestatis or gall-stones (Sherlock, 1968). An ultrasonic scan will demonstrate a choledochal cyst and will distinguish between these two common causes, by the identification in gall-stone jaundice of the dilated bile-ducts and perhaps a distended gall-bladder with gall-stones (Taylor *et al.*, 1974). In pregnancy this dilatation may be greater than usual, presumably because of the influence of the pregnancy hormone, relaxin. This effect was observed in a further patient, age 30 years, pregnant and with obstructive jaundice. The cause was an impacted common duct stone. The common duct was grossly dilated, measuring 2 cm in the antero-posterior diameter and 6 cm coronally. The dilatation was demonstrated with ultrasound and at surgery.

Because of the desire to minimize X-ray irradiation in pregnancy, ultrasonic scans are suggested as the initial radiological examination in the pregnant woman with obstructive jaundice. In all patients with a suspected choledochal cyst, ultrasonic scans should be made. There may be more than one cyst, or there may be associated cystic disease of the liver (Rothman, 1965).

REFERENCES

Alonso-Lej, F., Rever, W. B., and Pessagno, D. J., 1959. Congenital choledochal cyst. *International Abstracts of Surgery*, *108*, 1–30.

Chesterman, J. T., 1944. Choledochus cyst complicating pregnancy and the puerperium. *Journal of Obstetrics and Gynaecology of the British Empire*, *51*, 572–518.

Fleming, R. J., 1947. Cyst of the common bile duct in a case of pregnancy of eight months causing pyloric obstruction. *South African Medical Journal*, *21*, 778–782.

Lavenson, R. S., 1909. Cysts of the common bile duct. *American Journal of Medical Sciences*, *137*, 563–570.

Lichtman, S. S., 1953. *Diseases of the liver gall bladder and bile ducts*, p. 1246 (Kimpton, London).

Rothman, M. M., 1965. *Gastroenterology*, edited by Bochus, vol. 3, p. 600 (H. L. Saunders, London).

Sherlock, S., 1968. *Diseases of the liver and biliary system*, 3rd ed., p. 550 (Blackwell, Oxford).

Taylor, K. J. W., Carpenter, D. A., McCready, V. R., 1974. Ultrasound and scintigraphy in the differential diagnosis of obstructive jaundice. *Journal of Clinical Ultrasound*, *2*, 105–116.

1976, *British Journal of Radiology*, *49*, 427–429 MAY 1976

The limitations of $^{113}In^{m}$ for plasma volume measurement

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(Received November, 1975)

ABSTRACT

Previous authors have claimed that $^{113}In^{m}Cl_3$ is a valid tracer for plasma volume measurement. However, careful measurements in haematologically normal volunteers and in rabbits, using ^{125}I-labelled human serum albumin as a reference tracer, show that the results obtained with $^{113}In^{m}$-chloride, -citrate or -transferrin consistently overestimate the plasma volume and are probably no better than can be predicted from the height and weight of the subject.

Measurement of the circulating plasma volume using the indicator dilution principle entails measurement of the initial volume of distribution of one of the plasma proteins, usually albumin, which has been labelled with a suitable indicator. Early studies utilized dyes, notably T-1824 (Evans Blue) as *in-vivo* protein labels, but for practical reasons these have been largely superseded by ^{131}I- or ^{125}I-labelled proteins, in which the label is firmly incorporated into the protein molecule before injection. Recent revival of interest in the technique of radiocardiography for the measurement of cardiac output and related parameters (Veall *et al.*, 1954) has led a number of workers to explore the use of the short-lived radionuclide $^{113}In^{m}$ as a tracer for this purpose and incidentally as a plasma volume tracer (Hosain *et al.*, 1969; Wochner *et al.*, 1970; Parker *et al.*, 1974). These authors have concluded that $^{113}In^{m}$, injected as chloride in acid solution, binds quantitatively to circulating transferrin and provide a valid tracer for the measurement of plasma volume (except in those subjects in whom the serum iron-binding capacity is impaired) simply because there is a statistically significant correlation between the results of $^{113}In^{m}$ measurements and those utilizing radioiodinated albumin (RISA). However, inspection of the published data suggests that plasma volume measured with $^{113}In^{m}Cl_3$ is less accurate than would be expected for a measurement which is potentially capable of a high degree of precision (Davies, 1971).

This paper describes the comparison of $^{113}In^{m}Cl_3$ with ^{125}I-labelled albumin as a tracer for plasma volume and some further studies made with $^{113}In^{m}$ citrate as an alternative indicator.

METHODS

All estimations of plasma volume were carried out using ^{125}I-labelled albumin (^{125}I-HSA) as the reference tracer. $^{113}In^{m}Cl_3$ was injected simultaneously in eight volunteers, $^{113}In^{m}$ citrate in 14, and $^{113}In^{m}$-transferrin in a further two. Plasma volume was also measured in two rabbits using ^{125}I-HSA, $^{113}In^{m}$- transferrin and ^{59}Fe-transferrin.

Measurements in human subjects

1 μCi ^{125}I-HSA (Radiochemical Centre, Amersham, Code: IM 17P) and 20 μCi of the $^{113}In^{m}$ tracer were mixed, drawn up into a disposable syringe and injected intravenously over a period of about a minute as recommended by Hosain *et al.* (1969). $^{113}In^{m}Cl_3$ was obtained by elution from a generator (RCC, Code: TFC 3) with 0·05 mol/HCl. $^{113}In^{m}$ citrate was prepared from $^{113}In^{m}Cl_3$ by buffering with 5 per cent sodium citrate (B.P.) to give a solution of about pH 6·0. $^{113}In^{m}$-transferrin was prepared by adding $^{113}In^{m}Cl_3$ to a 100 μg/ml. solution of transferrin (Behringwerke AG, Germany) in 5 per cent sodium citrate (B.P.). Counting standards of the injected doses were made by 1:500 dilutions of aliquots of the injected doses in 1 per cent protein solution, with the addition of a few milligrammes of iodide or a trivalent cation (Cr^{+++}) as carrier.

Blood was taken without stasis from an antecubital vein in the arm opposite to that used for injection. 10 ml. samples were obtained at 10, 15 and 20 minutes post-injection. Radioactivity was measured in heparinized plasma using a scintillation counter with a 7·5×7·5 cm well-type sodium iodide crystal (LKB-Wallac 1280). A combination of differential decay and γ-spectrometry was used to separate the various radionuclides. All measurements of radioactivity were made to a precision (coefficient of variation) of 1·5 per cent or less, after corrections had been made for cross interference, background and decay (Veall, 1971). Plasma volume was calculated from measurements of radioactivity extrapolated to zero time.

Measurements in rabbits

1 μCi ^{125}I-HSA, 20 μCi $^{113}In^{m}$-transferrin and 2 μCi ^{59}Fe-transferrin were injected simultaneously into the ear vein of an anaesthetized rabbit. ^{59}Fe-transferrin was prepared by adding ^{59}Fe citrate (RCC, Code: IFS 2P) to a 100 μg/ml. solution of transferrin in sodium citrate. 1 ml. blood samples were taken from a femoral artery at frequent intervals up to 120 minutes post-injection. Radioactivity

TABLE I

ESTIMATES OF PLASMA VOLUME WITH ^{113}In ^{m} TRACERS AS PERCENTAGE OF VALUE OBTAINED WITH RISA

Study	Hosain *et al.*, 1969	Wochner *et al.*, 1970	Parker *et al.*, 1974	Present work	Present work
Tracer	$^{113}In^{m}Cl_3$	$^{113}In^{m}Cl_3$	$^{113}In^{m}Cl_3$	$^{113}In^{m}Cl_3$	$^{113}In^{m}$ citrate
Number of subjects	8	40	9	8	14
Mean	104·6	105	?	115	104
Range	96·3–113	88–128*	?	107–122	91·3–117
Correlation coefficient	0·69	?	0·79	0·96	0·95
p	$0{\cdot}05 < p < 0{\cdot}10$	?	$0{\cdot}01 < p < 0{\cdot}02$	$p < 0{\cdot}001$	$p \ll 0{\cdot}001$

* Estimated from published scattergram.

was measured in both heparinized blood and heparinized plasma as before.

RESULTS

Table I presents a summary of the results obtained in the present work and a comparison with the published data of other workers.

$^{113}In^{m}Cl_3$

The correlation between measurements of plasma volume with $^{113}In^{m}Cl_3$ and those with ^{125}I-HSA was good ($r = 0{\cdot}96$, $p < 0{\cdot}001$) in the eight subjects studied, but there was a consistent over-estimate of plasma volume with $^{113}In^{m}Cl_3$. The equation of regression was: $y = 1{\cdot}29x - 0{\cdot}49$.

$^{113}In^{m}$ *citrate*

The correlation between measurements of plasma volume with $^{113}In^{m}$ citrate and those with ^{125}I-HSA was also good ($r = 0{\cdot}95$, $p < < 0{\cdot}001$) in the 14 subjects studied, but the equation of regression was: $y = 0{\cdot}79x + 0{\cdot}76$.

$^{113}In^{m}$*-transferrin*

There was no better agreement between plasma volumes measured with $^{113}In^{m}$-transferrin and ^{125}I-HSA in the two subjects studied: values were 3·91 and 3·76 l. in one, and 3·33 and 2·96 l. in the other respectively.

Rabbit studies

In the two experiments in rabbits there was good agreement between plasma volume measured with ^{59}Fe-transferrin and ^{125}I-HSA, but poor agreement with that measured with $^{113}In^{m}$-transferrin. Figure 1 shows the rate of disappearance of these tracers from the plasma. The 20-minute delay in equilibration was attributed to poor mixing caused by administration of the anaesthetic. There was no difference between plasma volume estimated from the radioactivity measured in plasma samples and that derived from radioactivity in blood and the observed venous haematocrit (Table II).

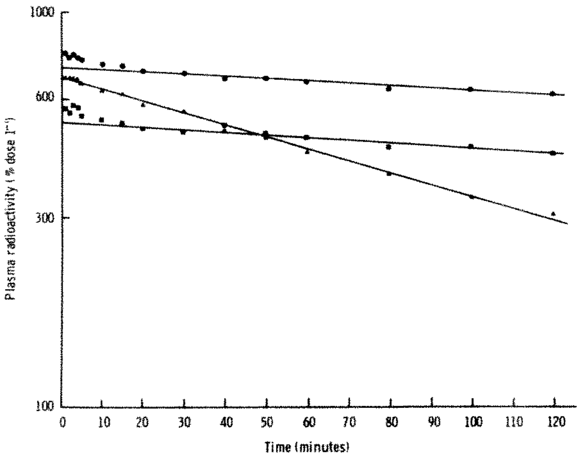

FIG. 1.

Plasma disappearance of ^{125}I-albumin (●), ^{59}Fe-transferrin (▲) and $^{113}In^{m}$-transferrin (■) after intravenous injection in the rabbit.

TABLE II

INITIAL VOLUMES OF DISTRIBUTION OF THREE INDICATORS IN THE RABBIT. VOLUME ESTIMATED FROM MEASUREMENTS OF RADIOACTIVITY IN PLASMA* AND IN BLOOD† AFTER CORRECTION FOR VENOUS HAEMATOCRIT

Indicator	Initial volume of distribution (ml.)*	Initial volume of distribution (ml.)†
^{125}I-albumin	140	142
^{59}Fe-transferrin	151	142
$^{113}In^{m}$-transferrin	191	188

Discussion

Our measurements of plasma volume in human subjects with ^{113}In^m tracers confirm their consistent overestimate of plasma volume in comparison with *I-albumin. There was a substantial overestimate of plasma volume, whether ^{113}In^m was administered as ^{113}In^{m}Cl$_3$, ^{113}In^m citrate or as ^{113}In^m-transferrin, implying rapid removal of some of the tracer from the plasma before complete mixing had occurred. The results of our experiments are consistent with an initial rapid release of ^{113}In^m from transferrin—followed, presumably, by the formation and subsequent phagocytosis of colloidal ^{113}In^m(OH)$_3$—and this is confirmed by the experiments in rabbits. An alternative possibility might be rapid uptake of ^{113}In^m by red blood cells, but this can be discounted since there was no difference between plasma volume measured with rabbit plasma, and that measured with rabbit blood and corrected for venous haematocrit.

That ^{113}In^m citrate gives better results than ^{113}In^{m}Cl$_3$ may be explained by the complexing action of the citrate preventing the formation of colloidal hydroxide, while the more physiological pH promotes binding to transferrin.

In conclusion, it is clear that ^{113}In^m is not a satisfactory substitute for *I-albumin if an accurate measure of plasma volume is required. The correlation between the ^{113}In^m results and those obtained with RISA in the present work is substantially better than that obtained by previous authors. Even so, the plasma volume estimates we obtain in haematologically normal people are only marginally better than can be predicted much more simply from the height and weight of the patient (Davies, 1971; Hurley, 1975).

Acknowledgments

The author thanks Dr. N. Veall for much helpful advice and discussion and Dr. J. Reeve for clinical collaboration. The author is also indebted to the volunteers who participated in this study.

References

Davies, J. W. L., 1971. Blood volume studies. Chap. 14 in *Radioisotopes in Medical Diagnosis*, Eds. E. H. Belcher and H. Vetter, pp. 319–341 (Butterworths, London).

Hosain, P., Hosain, F., Iqbal, Q. M., Carulli, N., and Wagner, H. N., Jun., 1969. Measurement of plasma volume using ^{99}Tc^m and ^{113}In^m labelled proteins. *British Journal of Radiology*, *42*, 627–630.

Hurley, P. J., 1975. Red cell and plasma volumes in normal adults. *Journal of Nuclear Medicine*, *16*, 46–52.

Parker, H., Weber, P. M., Van Dyke, D. C., Davies, H., Steele, P., and Sullivan, R., 1974. Evaluation of central circulatory dynamics with the radionuclide angiocardiogram. Chap. 4 in *Cardiovascular Nuclear Medicine*, Eds. H. W. Strauss, B. Pitt and A. E. James, pp. 67–100 (The C. V. Mosby Co., St Louis).

Veall, N., 1971. Multiple tracer techniques. Chap. 7 in *Radioisotopes in Medical Diagnosis*, Eds. E. H. Belcher and H. Vetter, pp. 158–170 (Butterworths, London).

Veall, N., Pearson, J. D., Hanley, T., and Lowe, A. E., 1954. A method for the determination of cardiac output (Preliminary report). In *Radioisotope Conference, 1954*, Eds. J. E. Johnston, R. A. Faires and R. J. Millett, vol. 1, pp. 183–192 (Butterworths, London).

Wochner, R. D., Adatepe, M., Amburg, A. V., and Potchen, E. J., 1970. A new method for estimation of plasma volume with the use of the distribution space of indium-113m-transferrin. *Journal of Laboratory and Clinical Medicine*, *75*, 711–720.

1976, *British Journal of Radiology*, *49*, 430–440

Analysis of dose, dose-rate and treatment time in the production of injuries by radium treatment for cancer of the uterine cervix*

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ABSTRACT

A retrospective study has been made of 15 patients who had developed severe complications to the bladder, rectum and ureters after radiation therapy for carcinoma of the cervix. Comprehensive dose distributions in the pelvis were calculated with computer assistance to visualize how the normal organs had been irradiated. The risk of normal tissue injury was analysed graphically with respect to the maximum radium dose, dose-rate and irradiation time.

The two groups of data representing the injured and non-injured organs separate much better in a dose-rate versus dose plot than in a conventional Strandqvist type dose-time plot. This implies that in radium therapy, the dose-rate, rather than the treatment time, is the important parameter in modifying the risk of normal tissue injury. Our results show a good separation of injured from non-injured cases only when the maximum values of dose and dose-rate were used. This suggests that clinically significant injury may develop from relatively small regions of high dose and dose-rate. Since the dose-rate varies from point to point in the pelvis (unlike treatment time), comprehensive determinations of dose-rate distributions are required in order to locate the sites of potential injuries.

For many years Paterson's isoeffect curve (Paterson, 1963), constructed on the basis of clinical experience with radium treatment of cancer of the tongue and floor of mouth, has been widely used to relate the biological equivalent dose for different treatment times in radium therapy for cancer of the uterine cervix. Although there are several studies of radiation injuries connected with radium therapy for cervical carcinoma (Paterson, 1963; Gray and Kottmeier, 1957; Strockbine *et al.*, 1970; Corscaden *et al.*, 1938, Chau *et al.*, 1962; Kottmeier and Gray, 1961; Fletcher *et al.*, 1958; Suit *et al.*, 1971; Joelsson 1970; Koeck and Hillsinger, 1971; Castro *et al.*, 1970; Fletcher *et al.*, 1966; Tod, 1947), only scattered data have been published that relate dose, dose-rate and treatment time to injury. There are no analyses, however, in which a clear distinction is made between dose-rate and overall treatment time in producing injuries by radium therapy.

In this investigation, we carried out a retrospective analysis of a small sample of radiation injury cases to study how the radium dose and treatment time, and also the radium dose and dose-rate, interact to produce injury to the bladder, rectum and ureters following intracavitary radium treatment for cervical carcinoma.

MATERIALS AND METHODS

The orthogonal radiographs (antero-posterior and lateral views of the radium applicator in the pelvis) and clinical records of 15 patients who had developed severe complications following radiotherapy for cervical carcinoma were obtained for dosimetric analysis. Table I summarizes the types of radiation injury each patient had sustained. Injury to the bladder, rectum and ureters were analysed with respect to the radiation distribution in these organs. For each patient, a computer was used to calculate in detail the three-dimensional distribution of the radium dose in the pelvis. Isodose contours were calculated in planes cutting through the posterior bladder wall, the ureters, and the anterior rectal wall. The purpose of these isodose plots was to look for the maximum radium dose received by each of the above organs in three-dimensional space. Also, characteristics of the radiation intensity near the organs could be quantified by calculating the dose gradient.

The dose distribution in a given plane was mapped on the computer output as an array of letters of the

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TABLE I

OUTLINE OF THE TREATMENT PLANS AND COMPLICATION FOR THE 15 PATIENTS

Case	Radium (mg–h)	External Beam dose (rad)	Complications		
			Ureters	Bladder	Rectum
1	5,990	3,000	+	0	0
2	5,040	0	+	0	0
3	8,400	5,300	+	+	0
4	4,300	4,000	+	+	0
5	6,900	0	+	+	0
6	6,000	3,300	+	0	0
7	11,440	3,500	+	+	0
8	10,320	4,000	+	0	0
9	7,200	0	0	+	+
10	6,600	4,000	0	+	0
11	5,250	3,900	0	+	0
12	9,000	3,000	0	+	0
13	6,000	3,000	0	0	+
14	7,150	0	0	0	+
15	6,020	3,000	0	+	+

Legends: + =injury; 0=no injury.

alphabets; each letter represented a certain dose-rate with an accuracy of ±10 per cent. An isodose curve was then drawn manually by tracing a smooth line through the identical letters. A complete isodose plot was done when all groups of identical letters in the array had been replaced by contour lines. Finally, shapes of the bladder, rectum, and ureters, along with the pelvic bone structures and the radium applicators as shown in the radiographs, were traced onto the isodose plots. The purpose was to illustrate how different organs in the pelvis were irradiated by the intracavitary radium. One complete set of such isodose plots is shown in Fig. 1.

The maximum radiation dose received by an organ from the radium sources was calculated by the product of the maximum radium dose-rate at the organ and the radium implant time. Since radium treatments are usually given in two sessions, the dose-rates used in the two treatments may not be the same. Therefore, the overall radium dose-rate at an organ was calculated as an average weighted dose-rate; the weighting factor was the irradiation time for each treatment. The dose-rate gradient at the site of interest was calculated as the increase in dose-rate from the site of interest to the next higher isodose curve divided by the separation distance.

Using the above methods of calculation, the maximum radium dose, dose-rate and dose-rate gradient for the bladder, rectum and ureters were calculated for all 15 patients. The calculation results are tabulated in Tables II, III and IV.

DATA ANALYSIS

Data tabulated in Tables II, III and IV, were used to correlate injuries to the bladder, rectum and ureters with the radium dose, dose-rate and treatment time. We emphasize that all patients included in this study have sustained injuries to one or, at the most, two of the three organs. The bladders, rectums and ureters in these 15 patients were classified into two groups, injured and non-injured. Maximum radium doses received by the injured bladders, rectums and ureters of the 15 patients were compared with the maximum radium doses received by the non-injured bladders, rectums and ureters in the same group of patients. This analytic method thus circumvents the need for a controlled group of patients with no injuries. Moreover, the variability in the biological response was probably minimized by using one group of patients for both the injured and non-injured organs.

DOSE-TIME RELATIONSHIPS

In Fig. 2, the maximum radium dose received by each organ is plotted against the treatment time. The bladder, rectum and part of the ureters were shielded by lead blocks during external beam treatments. The ensuing data analyses were therefore carried out with respect to radium-dose distribution only, assuming insignificant contribution to the total dose by external beam treatments. The radium dose-time combination that produced no noticeable damage to the normal organs is denoted by the symbols □ for the bladder, ○ for the ureters, and △ for the

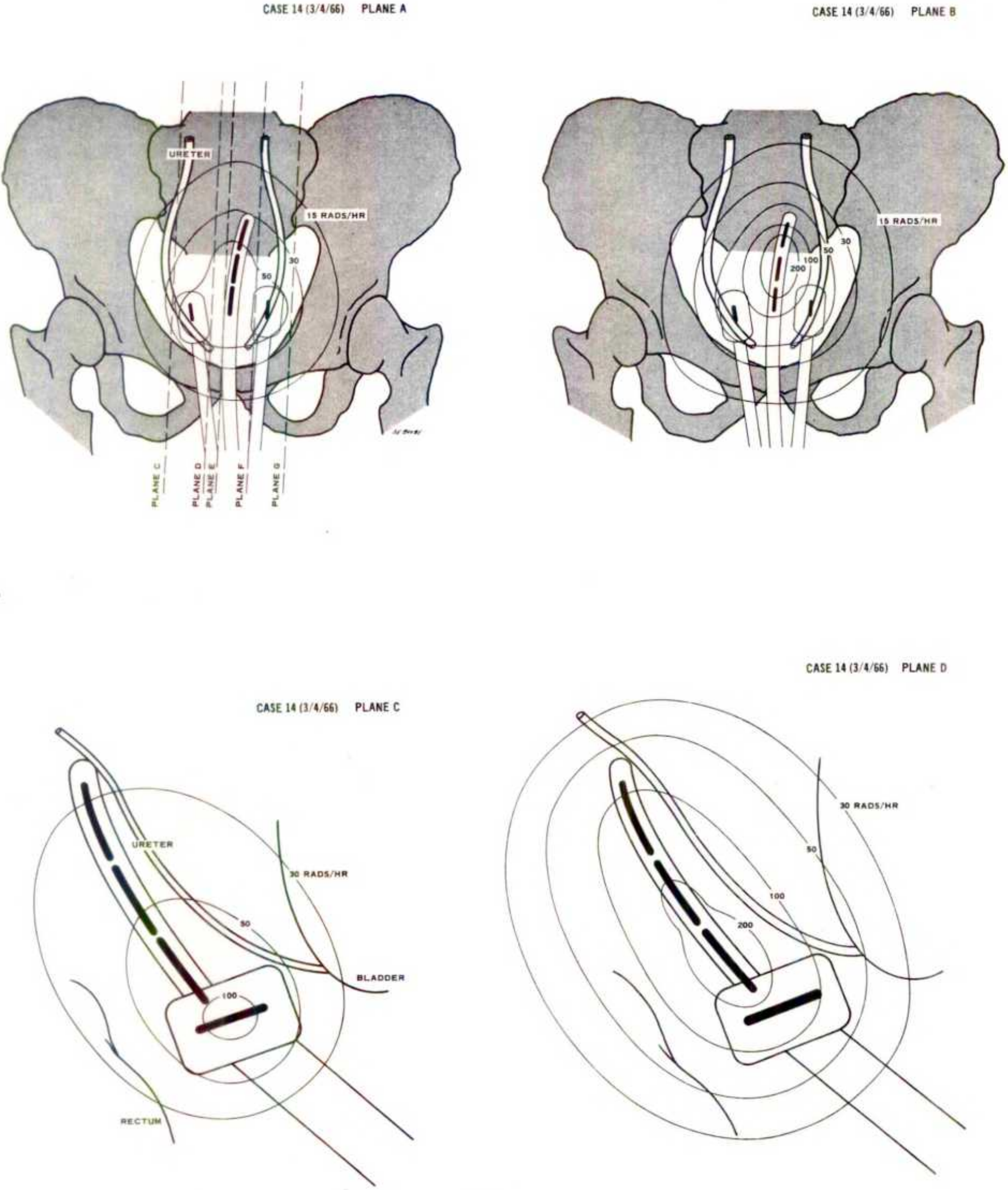

Fig. 1a
Composite isodose plot of dose-rate for Case 14. Sagittal planes shown on A.

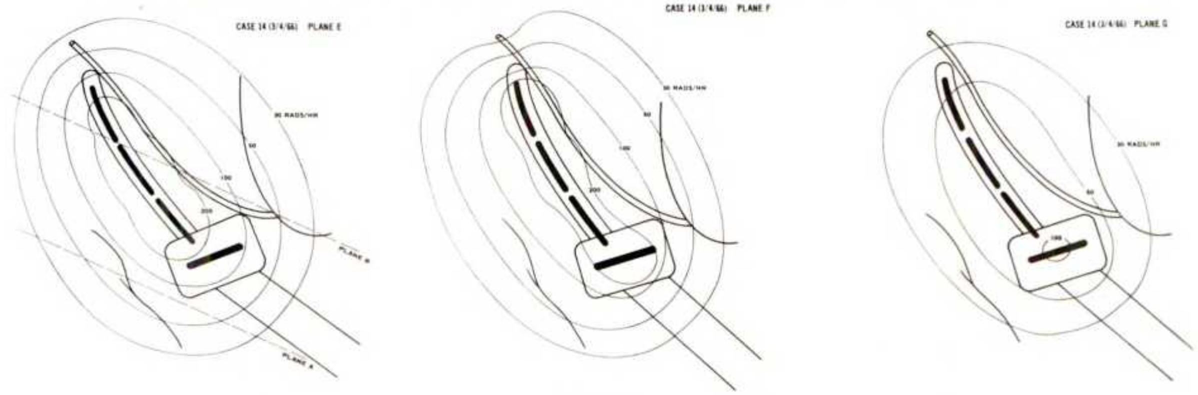

Fig. 1b.
Composite isodose plot of dose-rate for Case 14. Frontal planes shown on E.

TABLE II
Summary of the ureters dosimetry

Case	Max Ra dose (rad)	Time (h)	Ra dose-rate (rad/h)	Ra dose-rate Grad (rad/h/cm)	External beam dose (rad)	Radium (mg-h)
1*	5,800	86	68	51	3,000	5,990
2*	4,200	84	50	50	3,500	5,040
3*	5,200	112	46	16	5,200	8,400
4*	5,200	52	100	190	4,000	4,300
5*	5,300	53	100	48	0	6,900
6*	8,500	100	85	120	3,300	6,000
7*	9,600	144	67	20	3,500	11,440
8*	9,600	120	80	44	4,000	10,320
9	1,800	60	30	20	0	7,200
10	3,000	120	25	20	4,000	6,600
11	5,300	150	46	27	4,000	5,250
12	4,500	150	30	18	3,000	9,000
13	3,000	100	30	10	3,000	6,000
14	2,800	55	51	20	0	7,150
15	5,400	107	50	23	3,100	6,020

*Injury developed.

rectum. The dose-time combination that resulted in injury to an organ is denoted by a (×) superimposed on top of the symbol for the corresponding non-injured organ.

The dashed line drawn through the data points in Fig. 2 is one that best separates the two groups, injured and non-injured—best in the sense that the line minimizes the number of injured data points in the no-injury region, and vice versa. The goodness of separation technique (Kagan *et al.*, 1973) was used to calculate the Strandqvist curve that best separates the injured group from the non-injured. The optimum Strandqvist curve so constructed is represented by the equation $D = D_0 T^{+0\cdot3}$, where

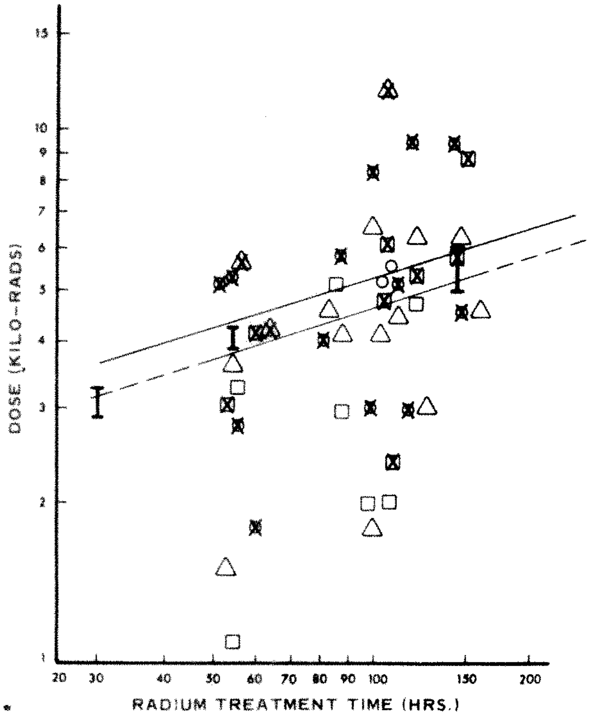

Fig. 2.

Separation of the injured and non-injured organs in a Strandqvist plot. The symbol □ = bladder, △ = rectum, and ○ = ureters. A symbol with a (×) superimposed on top of it represents injury to the organ.

D is the total dose, D_0 is an equivalent single dose, and T is the overall treatment time.

To compare the result of this small sample study with that of other investigators, the radium treatment protocols used in Stockholm, Manchester and Houston, which collectively represent a great deal of clinical experience, were superimposed onto the present dose-time data as shown in Fig. 2. The upper curve was constructed by Paterson (1963) based on his clinical experience with radium treatment of tumours of the oral cavity in Manchester. Interestingly, the Paterson curve appears to represent reasonably well the data that we have obtained by the analysis of injuries to the bladder, rectum and ureters.

The two vertical bars in the lower left portion of Fig. 2 are the dose-time protocols used at the Radiumhemmet in Stockholm, and the vertical bar in the upper right portion of the figure is the

TABLE III

Summary of the bladder dosimetry

Case	Max Ra dose (rad)	Time (h)	Ra dose rate (rad/h)	Ra dose-rate grad (rad/h/cm)	External beam dose (rad)	Radium (mg-h)
1	3,000	86	35	34	3,000	5,990
2	5,100	84	61	63	3,500	5,040
3*	2,400	112	21	16	1,800	8,400
4	1,200	52	23	69	0	4,300
5*	3,100	53	94	36	0	6,900
6	2,000	100	20	18	2,800	6,000
7*	5,800	144	40	31	0	11,440
8	4,800	120	40	24	0	10,320
9*	4,200	60	70	53	0	7,200
10*	5,400	120	45	150	0	6,600
11*	4,900	105	47	59	3,900	5,250
12*	9,000	150	40	110	0	9,000
13	2,000	100	20	21	3,000	6,000
14	3,300	55	60	39	0	7,150
15*	6,200	107	80	50	3,100	6,020

*Injury developed.

TABLE IV

SUMMARY OF THE RECTUM DOSIMETRY

Case	Max Ra dose (rad)	Time (h)	Ra dose-rate (rad/h)	Ra dose-rate Grad (rad/h/cm)	External beam dose (rad)	Radium (mg-h)
1	4,600	86	54	42	3,000	5,990
2	4,200	84	50	47	3,500	5,040
3	4,500	112	40	26	1,800	8,400
4	1,500	52	29	13	0	4,300
5	3,700	53	70	30	0	6,900
6	1,800	100	18	12	2,800	6,000
7	6,100	144	42	36	0	11,440
8	6,300	120	53	28	0	10,320
9*	4,200	60	70	66	0	7,200
10	3,000	120	25	39	0	6,600
11	4,200	105	40	37	3,900	5,250
12	4,500	150	30	18	0	9,000
13*	6,500	100	65	58	3,000	6,000
14*	5,500	55	100	115	0	7,150
15*	12,000	107	130	130	0	6,020

*Injury developed.

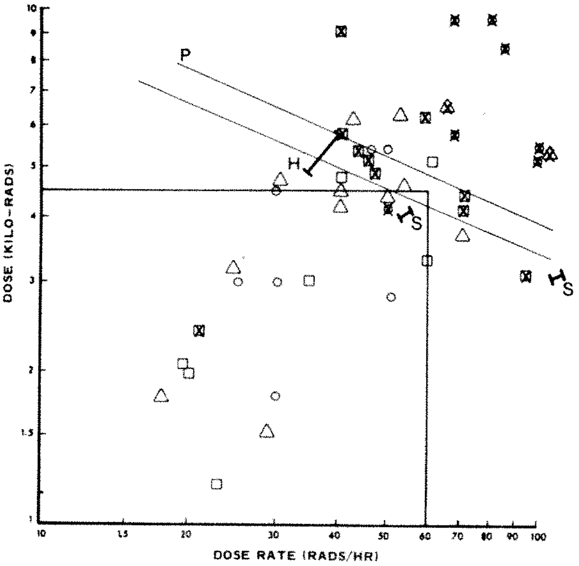

FIG. 3.

Separation of the injured and non-injured organs in the dose and dose-rate plot. The symbols, □=bladder, △=rectum, ⊙=ureters. A symbol with a (×) superimposed on top of it represents injury to the organ.
P=Paterson's dose—dose-rate curve.
S=Stockholm techniques.
H=Houston techniques.

corresponding dose-time relationship to the bladder commonly seen when using the Fletcher technique for cervical radium treatment. It is interesting to note that the optimum dose-time relationship implied by the four sets of data as shown in Fig. 2, all lie roughly in the belt that separates the injured and the non-injured groups in our small sample study.

Nevertheless, although it is gratifying that the protocols used in Manchester, Stockholm and Houston, are close to the best separation line drawn on the basis of a small sample of clinical data, the two sets of data points representing the injured and non-injured organs are poorly separated on the dose-time plot.

DOSE-RATE EFFECT

To investigate how dose-rate affects normal tissue damage in radium therapy, the maximum radium dose and dose-rate data in Tables II, III and IV are plotted in Fig. 3.

Distribution of the data points in Fig. 3 shows that the incidence of normal tissue injury is small when not more than 4,500 rad are given and the dose rates are below 60 rad/hour (1 rad/minute). This region of minimum injury risk is shown as a rectangular block in the figure. When the treatment régimes lie outside this block, the incidence of injury increases dramatically.

The upper line in Fig. 3 is Paterson's isoeffect curve plotted in a log dose-rate versus log dose plane. The bottom line drawn through the data points is one that best separates the injured and non-injured groups in the dose-rate versus dose plot. This line, constructed with the goodness of separation technique (Kagan *et al.*, 1973), has a $-0{\cdot}4$ slope on a log dose-rate versus log dose plot.

The two bars near the bottom of Fig. 3 are the dose and dose-rate protocols for the bladder and rectum utilized by the Stockholm technique, and the upper bar is the corresponding Houston technique for treating carcinoma of the cervix.

The relatively good separation of the two groups of data points in Fig. 3 is in sharp contrast to the poor separation in the dose-time plots of Fig. 2. This is particularly striking since the same set of data are used to plot Figs. 2 and 3.

This drastic improvement in the goodness of separation in a dose versus dose-rate plot, as compared to that in a dose-time plot, suggest dose-rate is a more important factor than the overall irradiation time in analysing tissue injury. It follows that the conventional Strandqvist dose-time plot is not as useful as the dose versus dose-rate plot for planning the optimum treatment strategy for radium therapy.

DISCUSSION OF RESULTS

The most important result of this small sample study is the discovery that the dose-rate versus dose plot gives rise to a much better separation of the injured and non-injured data points than a Strandqvist type dose-time plot. The superiority of dose-rate analysis is dramatically illustrated even with the present small sample of injury data. This implies that dose-rate is a more important parameter than the overall treatment time in analysing the risk of normal tissue injury. This result is consistent with clinical experience and radiation biology experiments. For example: the nominal standard dose (NSD) concept of Ellis (1968) which places less emphasis on treatment time (T) than fractionation number (N), *i.e.* $T^{\cdot 11}$ versus $N^{\cdot 24}$.

The low incidence of injury at dose-rates less than 60 rad/hour is compatible with the survival characteristics of Hela cells irradiated in culture (Hall, 1972). Below 60 rad/hour, the amount of cell killing depends on the total dose; the dose-rate shows little modifying effect on the cell survival for a given dose. Similarly the dose-rate effect on normal tissue injury is negligible below 60 rad/hour as shown in Fig. 3. When the radiation dose required to reduce a population of Hela cells to 10 per cent of its original number (10 per cent survival dose) is plotted against the dose-rate in a log dose versus log dose-rate plane, a line having a slope of $-0{\cdot}5$ results (Hall, 1972), representing the decrease of the 10 per cent survival dose with increasing dose-rate. The slope of the line as constructed from radiation biology data appears similar to the line that separates the injury and non-injury groups of data points shown in Fig. 3. Although we are comparing very different data the similarities in dose-rate dependence suggest that cell lethality depends on dose-rate in a very similar fashion whether the cell is in the rectum, bladder, ureter, the head and neck, or is in an established cell line *in vitro*.

Paterson's curve, Fig. 3, shows fair agreement with the optimum treatment regimens implied by our analysis and with that of the Houston technique in the dose-rate region of about 30 to 60 rad/hour. However, a recent report by Awwad *et al.* (1974) showed that recurrence tended to occur at treatment times below 72 hours when the total dose was reduced in accordance with Paterson's curve. Their work is consistent with ours in suggesting that the overall treatment time is not the important factor in modifying the effects of dose. Our work suggests rather that the local dose-rate is the important parameter. Although the average dose-rate does increase as the overall treatment time decreases, the local maximum dose-rates to tumour and to normal tissues may change in quite different ways depending on the details of the treatment procedure. Moreover, since dose-rate effects are strong only within the range of about 1 rad/minute to 100 rad/minute (Hall, 1972), as dose-rates to the tumours approach the upper limit and dose-rates to the normal tissues approach the lower limit of this range we may expect to find that dose-rate overall or treatment time are unimportant as dose modifying factors. In radium therapy as commonly applied, however, dose-rates tend to fall in the region where dose-rate effects are important and must be considered in treatment planning.

Finally, we want to emphasize that in our analysis of normal tissue injury, the stated dose is the maximum dose calculated to the organ by computer. When we examined the patient records, we found good correspondence between the site of injury and the site of high dose and dose-rate. In some cases, high dose and dose-rate were limited to only a small area in the affected organ. This is not unexpected since the isodose plots show that regions of high dose-rate are invariably accompanied by a steep dose-rate gradient. What is surprising is that the probability of normal tissue injury is high even when high dose and dose-rate are confined to relatively small "hot spots" in the affected organs.

An analysis of 50 documented cases of radiation injury in Stockholm (Joelsson, 1970) is shown in Figs. 4, 5, 6, and 7. As can be seen, separation lines on either the dose-time or dose versus dose-rate plots poorly separate the two sets of points representing injured and non-injured organs, respectively. This discrepancy with our results is disappointing. A possible reason for this discrepancy is as follows. Dosimetry for the 50 cases in Stockholm had been obtained from direct ionization chamber measurement in the bladder and rectum. Computer-assisted

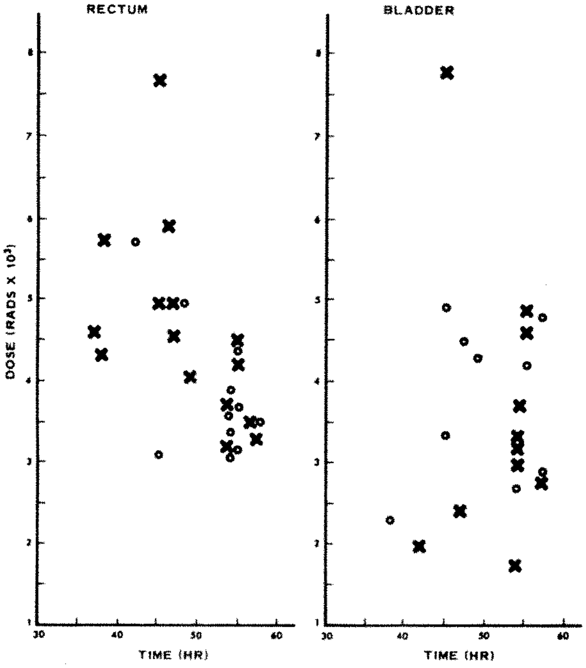

Fig. 4.

The injured and non-injured dose-time combinations in the 1958–59 series of patients in Stockholm are poorly separated. The symbol, ○, represents the no-injury dose-time combination, while the symbol × represents the injury dose-time combination.

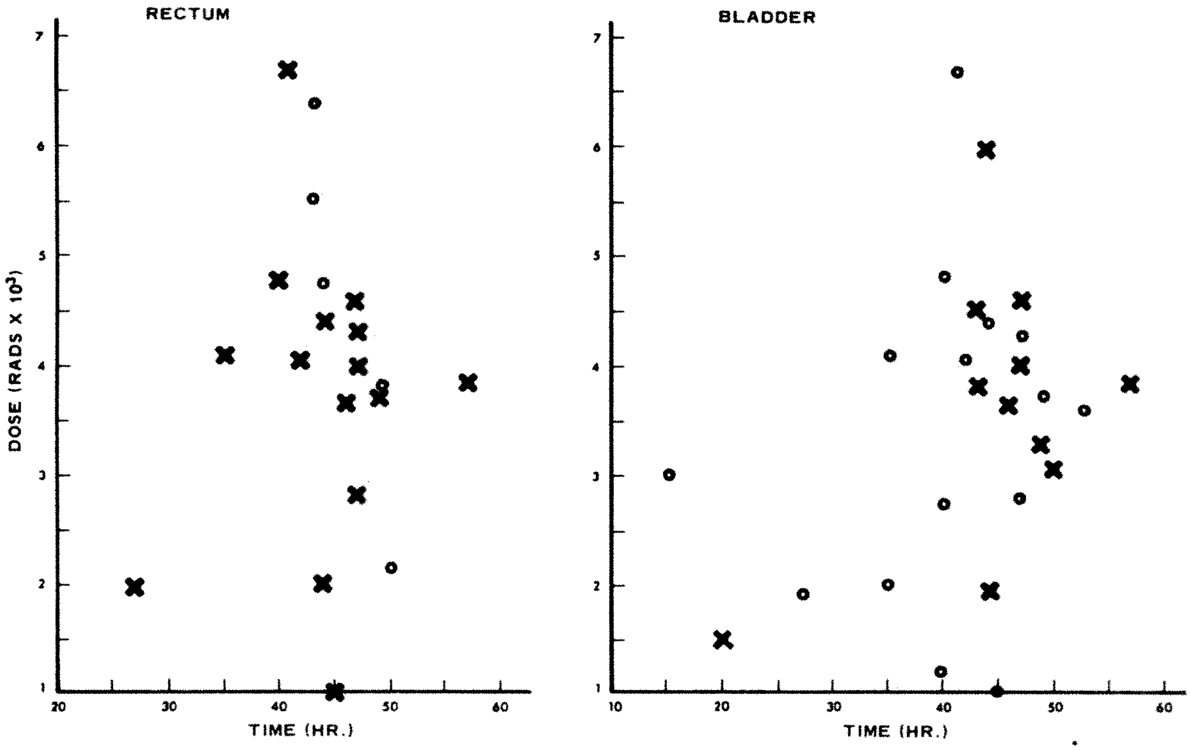

Fig. 5.

The injured and non-injured dose-time combinations in the 1962–66 series of patients in Stockholm are just as poorly separated as the 1958–59 series; ○ = no-injury dose-time combination, and × = injury dose-time combination.

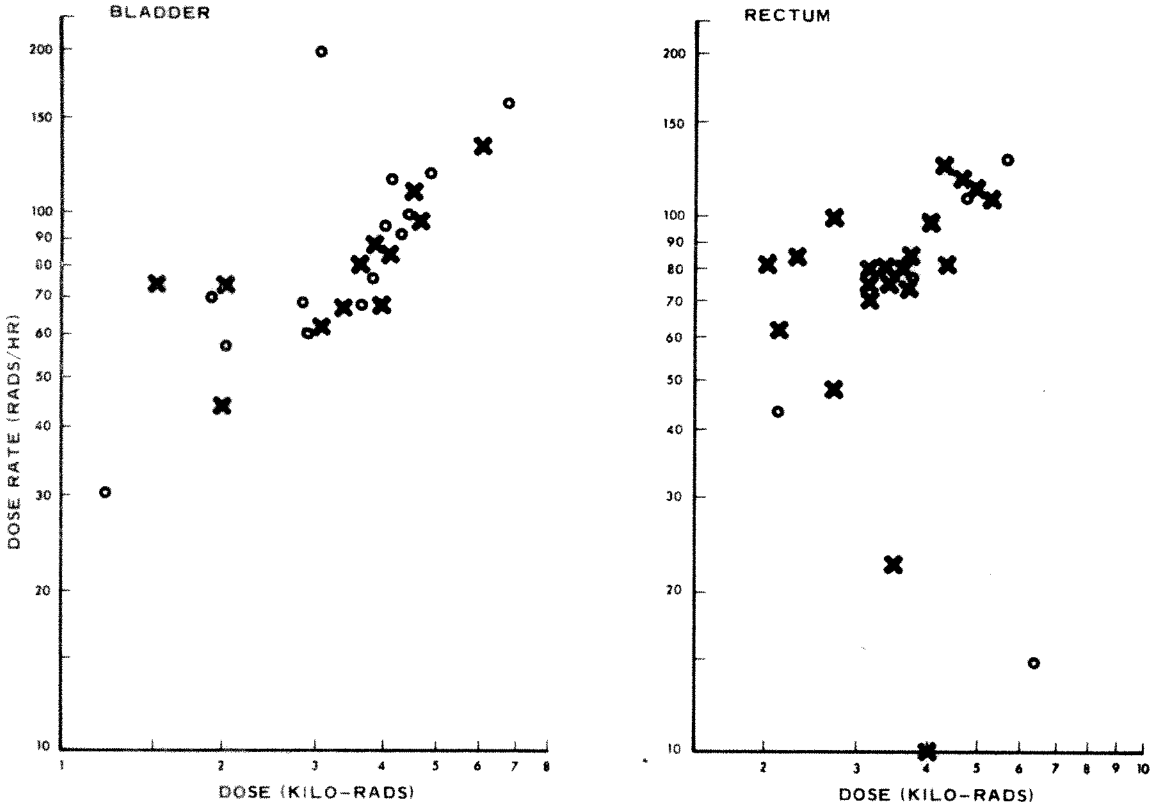

FIG. 6.

The dose and dose-rate combinations for the 1962–66 series of patients in Stockholm. There is no obvious separation between the two groups; ○ = no injury and × = injury.

dosimetry shows that in a region of high-dose-rate there is always a steep dose-rate gradient. If the reported chamber measurements are average values over a relatively large region of measurement—a common practice—the reported dose and dose-rate are not the maximum values to the affected organs. Our results show a good separation of injured from non-injured cases only when the maximum values of dose and dose-rate are used. The contrast between the Stockholm and our series of data points out that in injury analysis the important parameters are the maximum dose and dose-rate. This implies that regions of high dose and dose-rate can develop to clinically significant injury. It has been reported in the literature that the dose-rate gradient in the treatment volume should be carefully evaluated in radium treatment planning as the cure rate can be significantly influenced by the steepness of the dose-rate gradient in the target volume (Awwad, *et al.*, 1974).

Given these recent clinical and radiation biology data, it appears that radium treatment plans should be based on dose-rate and dose-rate gradient rather than the overall treatment time. The similarity in the optimum dose dose-rate relationships for minimizing injury to normal tissues in the pelvis and in the head and neck regions brings up the possibility that in all cases we may be dealing with injury to a common tissue type. We postulate that this tissue type is the connective tissue which apparently responds more or less with the same sensitivity to radiation regardless of its site.

The demonstration that the dose-rate rather than the overall treatment time is the important parameter in estimating the risk of injury for a given radium dose makes it necessary to obtain accurate data on the dose-rate distributions within the patient. Since the dose-rate changes from point to point in the treatment volume (unlike the overall treatment time which remains constant), comprehensive calculation of the dose-rate distribution by computer may be necessary in order to detect potential sites of injury. However, we must bear in mind that the resulting dose distribution is meaningful

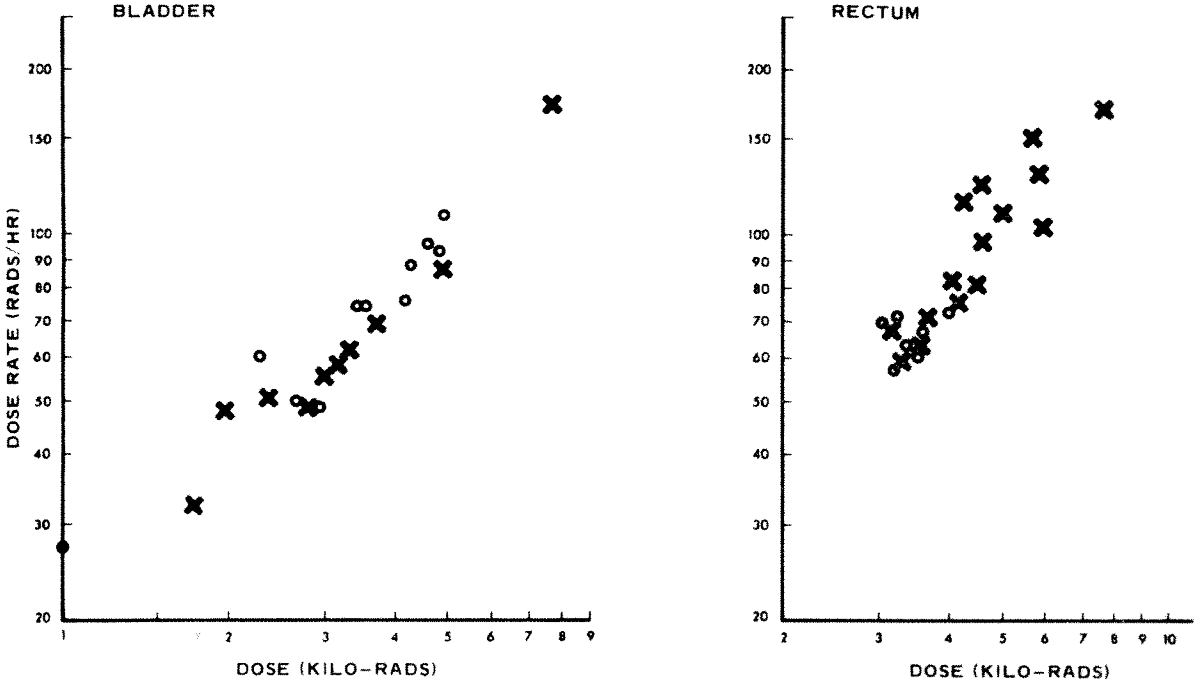

Fig. 7.

Display of the injured and non-injured dose and dose-rate combinations for the 1958–59 series of patients in Stockholm. There is also no obvious separation between the injured and non-injured groups; ○=no injury, ×=injury.

only if every step in taking the radiographs and extracting information from them for computer calculations are carefully controlled.

Summary

Dose-rate rather than overall treatment time is the important parameter in modifying the effect of dose in radium therapy. It should be stressed more than the overall treatment time in estimating the risk of normal tissue damage. Relatively small "hot spots"—regions of high dose and dose-rate—can become the foci of clinically significant radiation injury. These results imply that comprehensive calculations of the dose-rate distribution, as is possible with computer assistance, are necessary in order to identify potential sites of injury.

REFERENCES

Awwad, H. K., Burgers, J. Marion V., and Marcuse, H. R., 1974. The influence of tumor dose specification of the early clinical results of interstitial radium tongue implants. *Radiology*, *110*, 177–182.

Castro, J. R., Issa, P., and Fletcher, G. H., 1970. Carcinoma of the cervix treated by external irradiation alone. *Radiology*, *95*, 163–166.

Chau, P. M., Fletcher, G. H., Rutledge, F. N., and Dodd, G. D., 1962. Complications in high dose whole pelvis irradiation in female pelvic cancer. *American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine*, *87*, 22–40.

Corscaden, J. A., Kasabach, H. H., and Lenz, M., 1938. Intestinal injuries after radium and roentgen treatment of carcinoma of the cervix. *American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine*, *39*, 871–894.

Ellis, F., 1968. The relationship of biological effect to dose-time-fractionation factors in radiotherapy. In *Current Topics in Radiation Research*, edited by M. Ebert and A. Howard, Vol. 4, pp. 359–397 (North Holland Publishing Co., Amsterdam).

Fletcher, G. H., Brown, T. C., and Rutledge, F. N., 1958. Clinical significance of rectal and bladder dose measurements in radium therapy of cancer of the uterine cervix. *American Journal of Roentgenology*, *79*, 421–449.

Fletcher, G. H., Watanavit, T., and Rutledge, F. N., 1966. Whole pelvis irradiation with 4,000 rads in Stage I and Stage II cancers of the uterine cervix. *Radiology*, *86*, 436–443.

Gray, M. J., and Kottmeier, H. L., 1957. Rectal and bladder injuries following therapy for carcinoma of the cervix at the Radiumhemmet. *American Journal of Obstetrics and Gynecology*, *74*, 1294–1303.

Hall, E. J., 1972. Radiation dose-rate: a factor of importance in radiobiology and radiotherapy. *British Journal of Radiology*, *45*, 81–97.

Joelsson, I., 1970. Radiotherapy of carcinoma of the uterine cervix with special regard to external irradiation. *Acta Radiologica, Supplementum 302.*

Kagan, A. R., Lee, K. H., Wollin, M., and Norman, A., 1973. An examination of some dose-time relationship in therapeutic radiology. *British Journal of Radiology*, *46*, 354–359.

Koeck, G. P., and Hillsinger, W. R., 1971. Dosage tolerance of pelvic structures with cobalt-60 rotation therapy. *American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine, 111*, 260–268.

Kottmeier, H. L., and Gray, M. J., 1961. Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix, a 5-year follow-up. *American Journal of Obstetrics and Gynecology, 82*, 74–82.

Paterson, R., 1963. *The Treatment of Malignant Disease by Radiotherapy*, pp. 210 (Edward Arnold, London).

Strockbine, M. F., Hancock, J. E., and Fletcher, G. H., 1970. Complications in 831 patients with squamous cell carcinoma of the intact uterine cervix treated with 3,000 rads or more whole pelvis irradiation. *American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine, 108*, 293–304.

Suit, H., Brown, D. B., Withers, H. R., and Thompson, J., 1971. Consideration of dose rate in intracavitary radiation therapy systems. In *Afterloading in Radiotherapy Proceedings of a Conference Held in New York, City May 6–8, 1971*, edited by H. Simon, pp. 230–243.

Tod, M. C., 1947. Optimum dosage in treatment of cancer of the cervix by radiation. *Acta Radiologica, 28*, 564–575.

Book review

Fast Processes in Radiation Chemistry and Biology. Edited by Gray, Fielden and Michael, pp. 381, 1975 (Institute of Physics, John Wiley & Sons), £11·50.

This is the proceedings of the 5th L. H. Gray Conference held at the University of Sussex in September 1973. The central theme, which is the title of the book, brought together a distinguished group of chemists, physicists and biologists who have been using, and perfecting, analytical methods of studying fast, and some *very* fast, reactions. The first section assembles the papers on techniques—apparatus for generating *picosecond* pulses of electrons or of light, ways of bringing ESR measurements, normally a slow technique, into the microsecond range and of using conductivity as an indicator in following pulse radiolysis experiments where charged species are involved. The second chapter deals with the applications of these methods in general chemistry, the third in biochemistry. Chapter 4 is devoted to fast reactions involving nucleic acids, and Chapter 5 to work with enzymes and proteins. The sixth and final chapter reports experiments involving whole cells. The picosecond experiments—both with single electron bunches and with laser flashes—are very impressive, if somewhat restricted in the systems they can examine. Of great interest is the imaginative way in which fast processes in micelles and membranes are now being studied by means of fluorescent probes incorporated into their structure. Another field which is opening up is the identification of the residues in the active sites in enzymes by using the secondary radicals formed by pulse radiolysis of an appropriate solute as probes which react selectively with particular amino acids. Superoxide dismutase is a particularly interesting enzyme since its substrate, O_2, can be produced virtually instantaneously in any desired concentration by an electron pulse to the enzyme solution and the kinetics of the enzyme-substrate reaction followed in detail. The three papers on intact cells (spores and bacteria) illustrate the relevance of the fast chemistry discussed in earlier chapters to the ultimate radiation damage observed.

This collection of papers from a small conference with a limited topic should retain its value and interest much longer than the proceedings of most large international meetings.

J. W. Boag.

1976, *British Journal of Radiology*, *49*, 441–449 MAY 1976

Mathematical derivation of optimal treatment schedules for the radiotherapy of human tumours. Fractionated irradiation of exponentially growing tumours

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(Received July, 1975)

ABSTRACT

A mathematical model is developed to allow derivation of optimal treatment schedules for the radiotherapy of exponentially-growing tumours. Preliminary calculations based on available data suggest that optimal schedules would (in general) be more protracted than conventional schedules and might achieve a significantly better tumour cell kill without causing excessive damage to normal connective tissue.

The model is too simple, and the data inadequate, for the conclusions reached to be used as a guide to clinical practice at present. However, the analysis can be extended to more realistic models which may be of clinical benefit when the appropriate data can be obtained.

Very little reliable information has been obtained on the radiobiology or growth kinetics of human tumours. Nevertheless, it is commonly assumed that when such information is obtained, the logical design of optimal treatment schedules, superior in effect to existing schedules, will become a real possibility. Indeed, this sometimes unspoken assumption provides the motivation for much current research on radiobiology and on cell-population kinetics.

There are some difficulties, however. It is, in the first place, by no means guaranteed that ethically acceptable methods of characterizing particular human tumours will ever be found. Should such methods elude us permanently, there is no alternative to empiricism in seeking better treatment schedules.

Even if this obstacle can be overcome, the identification of optimal schedules may not be a straightforward matter, nor even a possibility. Industrial control processes provide many examples of optimization problems which are beyond the capacity of mathematics and computer science at the present time. Might not biological optimization problems prove equally intractable?

Finally, neither the availability of suitable data nor solution of the relevant mathematical problems provides any guarantee that the effort will have been worth while. Perhaps optimal schedules will turn out to be only marginally better than conventional schedules in current use.

In this paper, which is the first of a series, we examine an approach to two of the three problems mentioned—the derivation of optimal schedules from primary data, and the assessment of the clinical benefits which optimal schedules may be expected to provide.

We introduce here a primary model which is used to derive optimal schedules for the particularly simple case of exponentially-growing tumours and draw on the small amount of data available to compute actual schedules and their effects for some hypothetical situations. The primary model and the derivation for exponentially-growing tumours provide the basic groundwork for the examination of more realistic situations. In subsequent papers we will extend the analysis to deal with Gompertzian tumour growth, variations in the growth fraction, the kinetics and radiobiology of oxygenated and hypoxic cells and the use of non-uniform treatment schedules.

By examining a succession of increasingly realistic models, built up as a hierarchy with the primary model as its base, we hope to arrive at principles of optimal radiotherapy which may be of sufficient generality to be clinically useful. As Fowler has commented: "We must hope that certain broad principles will emerge in order that we may deduce statistically better ways of treating cancer in certain sites without having to measure all the cell population parameters in each tumour individually" (Fowler, 1966).

The hierarchal strategy mentioned above differs from the strategy of other workers who have examined mathematical models of fractionated radiotherapy (Cohen, 1973; Fischer, 1971; Steward and Hahn, 1971; Hethcote and Waltman, 1973) in that the final results of optimal search at any level of the hierarchy define the starting position for optimal search at the next level. This should allow a rational approach to analytically intractable models whose complexity might otherwise reduce optimal search to the simulation of tens of thousands of fractionation patterns with random permutations of large numbers of parameters—an approach scarcely better than empiricism.

It must be emphasized very strongly that the optimal schedules which we derive in the present paper are essentially illustrations and are certainly not intended to justify radical departures from presently-accepted clinical practice. Considerably more realistic models and very much better data will be necessary before clinical relevance can be claimed.

Meantime, we hope the present analysis will prove instructive.

ASSESSMENT OF RADIATION DAMAGE TO NORMAL CONNECTIVE TISSUE: THE CRE SYSTEM

A logical prerequisite for consideration of optimal radiotherapy is some means of assessing radiation damage to the normal tissue or tissues whose radiation tolerance limits the number of fractions which can be safely given. Usually, though not invariably, normal connective tissue is the limiting tissue in clinical radiotherapy, and we confine attention to this case.

The accumulation of biological radiation damage to a composite tissue is a complex process for which empirical or semi-empirical descriptions constitute the best representations presently available (Ellis, 1969; 1971; Liversage, 1971; Kirk *et al.*, 1971; Orton and Ellis, 1974). In this analysis we make use of the cumulative radiation effect (CRE) system of assessment which has been developed by Kirk *et al.* (1971) as an extension and a generalization of the nominal standard dose (NSD) concept proposed by Ellis (1969; 1971). Though conceptually similar to the NSD, the CRE differ in that it can be applied to all subtolerance levels of radiation injury, not only at the point of tolerance. As will be seen, this feature of the CRE system provides the key to the extension of the present analysis to more realistic models.

Consider, the simplest case, that of a uniform schedule of N fractions, each of d rad, each fraction (excluding the first) being administered on the t^{th} day after its immediate predecessor. On the CRE system for fractionated irradiation (Kirk *et al.*, 1971) a scalar index (R_f) of connective tissue damage is defined and can be expressed as:

$$R_f = d \, . \, N^{a} \, . \, t^{-b} \qquad . \quad . \quad . \ (1)$$

where a and b are constants, found to have values of 0·65 and 0·11 respectively. This formula holds reasonably well for levels of damage up to and including tissue tolerance the R_f value for which (although depending on a number of factors) is frequently found to be around 1800.

Rearranging equation (1) we can write

$$N = \left(\frac{R_f}{d}\right)^{1/a} . \, t^{b/a} \qquad . \quad . \quad . \ (2)$$

which defines the (not-necessarily integer) number of fractions which must be given on the schedule concerned in order to reach the level of connective tissue damage indicated by the chosen R_f value.

Of course, it is intuitively improbable that the complex processes of tissue damage and recovery can be adequately represented by a simple algebraic relationship between four scalar quantities (see Kirk 1976; Kirk *et al.*, 1976). Indeed, it has recently been claimed that the NSD formula is inaccurate to a clinically significant extent (Berry *et al.*, 1974), though the experimental basis for this conclusion has been questioned (Orr, 1974; Orton, 1975) and it is not supported by the observations of Turesson and Notter (1975).

Probably, the NSD/CRE formulae are first-order scalar approximations to more complex multidimensional relationships. The inexact nature of the approximations will no doubt become apparent as more varied patterns of therapy are explored. This potential source of error must be borne in mind when unconventional schedules are under consideration.

At present the NSD/CRE formulae are the best estimators of tissue damage that we have, and the CRE system will be used for this purpose throughout the paper.

THE PRIMARY MODEL FOR OPTIMAL RADIOTHERAPY OF EXPONENTIALLY GROWING TUMOURS

Consider now the radiation damage sustained by the tumour. Since the conscious aim of radiotherapy is the total elimination of all clonogenic tumour cells it seems reasonable to choose the clonogenic surviving fraction as a suitable index by which to assess radiation damage to the tumour.

For a homogeneous population of clonogenic cells, the clonogenic surviving fraction (σ) after administration of a single radiation dose of d rad can often be expressed as

$$\sigma = 1 - (1 - e^{-d/D_0})^{n} \qquad . \quad . \quad . \ (3)$$

where D_0 and n are the mean lethal dose and the extrapolation number (respectively), parameters characteristic of the survival curve for the cells concerned, and of the radiation quality employed (Elkind and Whitmore, 1967). This gives a survival curve with zero initial slope. Recent work indicating a non-zero initial slope may necessitate a more sophisticated representation (see Alper, 1975).

Suppose now that clonogenic cells are instantaneously killed (or sterilized) by each fraction of the radiation dose but that in the time between fractions the surviving clonogenic cells proliferate exponentially with doubling time τ days, and hence with growth constant $\lambda = \frac{0{\cdot}693}{\tau}$ (days)$^{-1}$.

Consider a uniform schedule of fractionated irradiation, the first fraction being given on day zero, the second on day t, the third on day $2t$ and so on, the K^{th} fraction being given on day $(K\text{–}1)t$. We introduce the following notation: let $Q_1, Q_2 \ldots Q_K$ be sizes of the cell population immediately *before* administration of the 1st, 2nd . . . K^{th} fraction respectively while $Q_1', Q_2' \ldots Q_K'$ are the corresponding cell population sizes immediately *after* the same fractions have been given.

Then since the population is always attenuated by a factor σ whenever a fraction is given, but is always amplified by a factor $e^{\lambda t}$ between successive fractions, we have the following set of relationships:

$$\begin{aligned} Q_1' &= \sigma Q_1 \\ Q_2' &= \sigma Q_2 = \sigma e^{\lambda t}\, Q_1' = (\sigma)^2\, e^{\lambda t} . Q_1 \\ Q_3' &= \sigma Q_3 = \sigma e^{\lambda t}\, Q_2' = (\sigma)^3\, e^{2\lambda t} Q_1 \\ Q_K' &= \sigma Q_K = \sigma e^{\lambda t} Q'_{K-1} = (\sigma)^K e^{\lambda (K-1) t} Q_1 \end{aligned} \qquad (4)$$

If the K^{th} fraction happens to be the last one in the schedule then Q_K is the final surviving fraction of clonogenic tumour cells and is the obvious figure of merit to consider when deriving optimal schedules.

However, the asymmetry of K and $(K\text{–}1)$ in the terms $(\sigma)^K$ and $e^{(K-1)t}$ makes for mathematical difficulties which we can best circumvent by employing a device referred to by Bellman (1957) as "approximation in policy space" *i.e.* the optimization of some quantity which is approximately but not identically the same as the quantity whose optimization is intended. In this case we deal not with Q_K but with Q_K' *i.e.* the population size time t after the last fraction) which we shall now describe as Q_f the effective *final* clonogenic population at the end of treatment (see Fig. 1 for a clarification of the preceding discussion). This makes for mathematical simplicity without materially affecting the end result.

The fraction of clonogenic cells surviving the whole treatment schedule may then be expressed as

$$\left(\frac{Q_f}{Q_1}\right) = (\sigma)^{.K} e^{\lambda K t} \qquad . \qquad . \quad (5)$$

Using equation (3) to substitute for σ and equation (5) to substitute for K (now identified with N) we obtain

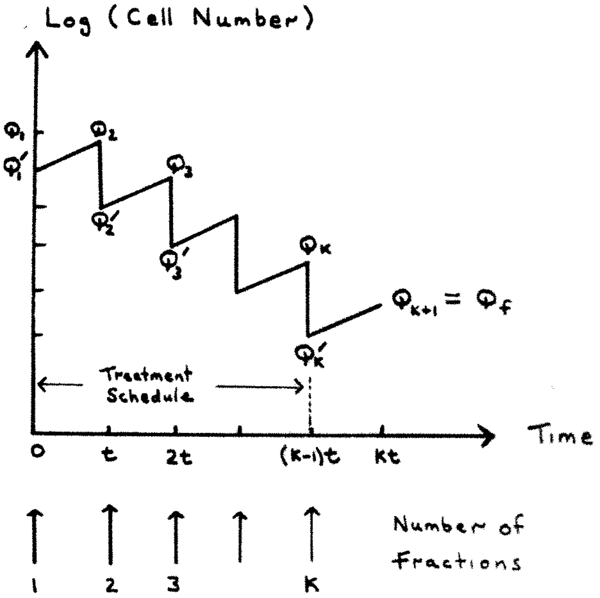

FIG. 1.
Decline of tumour population with successive fractions.

$$\left(\frac{Q_f}{Q_1}\right) = \left[\, 1 - (1 - e^{-d/D_0})^n \,\right]^{\left(\frac{R_f}{d}\right)^{1/a} t^{\,b/a}} \;.\; e^{\lambda \left(\frac{R_f}{d}\right)^{1/a} t^{\,(1+b/a)}} \qquad . \quad . \quad . \quad . \quad . \quad (6)$$

which gives the final surviving fraction in terms of:

(a) parameters (a, b, R_f) which refer to radiation damage to normal connective tissue;
(b) parameters (n, D_0, λ) which refer to the radiobiological and kinetic properties of the tumour;
(c) parameters (d, t) which define the treatment schedule given.

We now seek *optimal* schedule parameters (d^*, t^*) such that the surviving fraction $\left(\frac{Q_f}{Q_1}\right)$ is *minimized.*

Mathematically, this means that the equations

$$\frac{\partial}{\partial t} \cdot \left(\frac{Q_f}{Q_1}\right) \Bigg|_{t=t^*} = 0 \qquad . \qquad . \quad (7)$$

and

$$\frac{\partial}{\partial d} \cdot \left(\frac{Q_f}{Q_1}\right) \Bigg|_{d=d^*} = 0 \qquad . \qquad . \quad (8)$$

and the inequalities

$$\frac{\partial^2}{\partial t^2} \cdot \left(\frac{Q_f}{Q_1}\right) \bigg|_{t=t^*} > 0 \qquad . \qquad . \ (9)$$

$$\frac{\partial^2}{\partial d^2} \cdot \left(\frac{Q_f}{Q_1}\right) \bigg|_{d=d^*} > 0 \qquad . \qquad . \ (10)$$

are simultaneously satisfied.

With $\left(\frac{Q_f}{Q_1}\right)$ defined by equation (6) we can solve equations (7) and (8) to obtain t^* and d^* which, provided these values also satisfy the inequalities (9) and (10) define the optimal treatment schedule which, for a given value of R_f, gives the smallest possible surviving fraction. Though elementary in principle, this procedure involves some rather tedious algebra and we here state only the results—which can, of course, be verified directly.

By partially differentiating equation (6) with respect to t and equating the resultant expression to zero we find

$$t^* = -\frac{\ln\left[1-(1-e^{-d/D_0})^n\right]}{\lambda\,(1+a/b)} \ . \qquad . \ (11)$$

$$= -\frac{\ln\left[1-(1-e^{-d/D_0})^n\right]}{\ln 2\,.\,(1+a/b)} \,.\, \tau \qquad . \ (12)$$

It must be noted at once that this relationship is only physically meaningful if it asserts a real positive value of t^*, which is not the case for $n=1$. The case of a "shoulderless" survival curve does indeed turn out to be rather special and we choose to ignore it in this first paper. An analysis of the "shoulderless" survival curve will be presented in due course (Kirk and Wheldon, in preparation).

Confining attention to the more common situation where $n>1$ (*i.e.* a "shouldered" survival curve), we can substitute t^* into equation (12) from equation (11), differentiate equation (12) with respect to d, set to zero and so obtain the somewhat formidable equation

$$D_0\,\phi\, n\, l\phi = -(a+b)\,(1-\theta)\,\theta^{n-1} n d^* \qquad . \ (13)$$

where $\theta = 1 - e^{-d^*/D_0}$ . . . . . (14)

and $\phi = 1 - \theta^n$ . . . . . (15)

Since equation (13) is not analytically soluble we must have recourse to numerical analysis using a digital computer, in order to evaluate d^* and hence (by substitution back into equation (12)) obtain the optimal parameters (d^*, t^*) together. Using a Newton-Raphson method of root location it was found that for a wide range of values of D_0 and n (with $a=0{\cdot}65$, $b=0{\cdot}11$) d^* and D_0 were linearly related for any fixed value of n. The solution is therefore of the general form

$$d^* = F(n)\,.\,D_0 \quad . \quad . \quad . \ (16)$$

where $F(n)$ is a function which must be evaluated numerically.

The linear relationship (for fixed n) between d^* and D_0 complements the linear relationship between t^* and T (for fixed n) which is asserted by equation (12). These two relationships allow us to draw families of straight lines which permit optimal parameters to be read off graphically.

Two families of lines are depicted in Figs. 2 and 3 and enable the identification of optimal schedules for a range of values of n, D_0 and τ.

Comparison of Optimal and Conventional Schedules

Having derived a method for the identification of optimal schedules, it would be instructive to compare the effects of optimal and conventional schedules for some numerical cases.

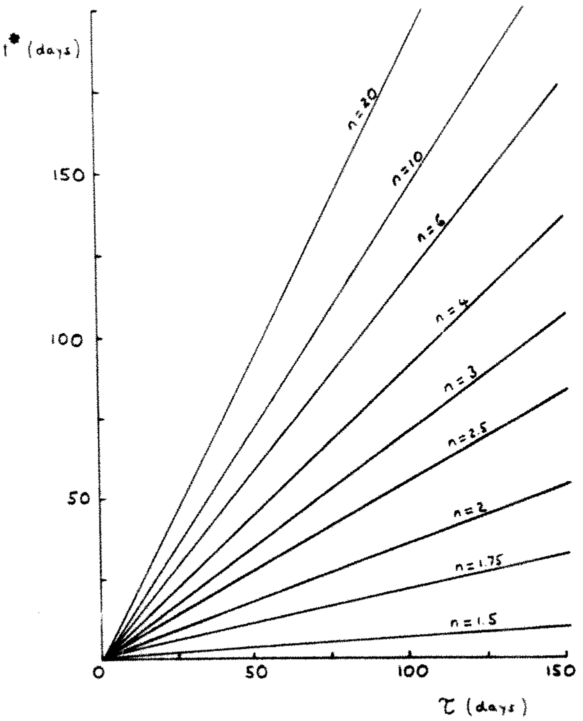

Fig. 2.

Relationship between the optimal time interval between fractions, t^* (days), and the tumour doubling time, τ (days), for various values of the extrapolation number, n.

As has been stressed previously, existing human data are inadequate to support reliable calculations at the present time. We shall, however, solely for illustrative purposes, consider a number of hypothetical examples, examining tumours with properties thought to be "typical" as well as some more specialized examples.

Survival curve parameters for human cell lines vary widely. However, we have selected $n=2$ and $D_0=150$ rad as "typical" values which are representative of a large number of the human cell lines which have been examined (Whitmore and Till, 1964; Fowler, 1966; Elkind and Whitmore, 1967).

Volume-doubling times present a problem in that they are seldom measurable when the tumour is microscopic, and values obtained for macroscopic tumours are unlikely to hold for microscopic tumours, since tumour growth is more often Gompertzian than purely exponential (Mendelsohn, 1963; Laird, 1964; 1965; Steel and Lamerton, 1966; Salmon, 1971; Bichel, 1971). This feature will be further considered below.

Nevertheless, it is striking that many human tumours do seem to grow very slowly. Tubiana reviewed a number of cases and concluded that the mean doubling time for a macroscopic primary carcinoma in man was around 70 days, though the range of variation was considerable (Tubiana, 1971).

Table I shows the features of optimal schedules for parameter values of $n=2$, $D_0=150$ and a range of volume-doubling times from 10 to 130 days. The cell-kill effect of the optimal schedules is given in Table II, which also shows the effect of a more conventional schedule (30 fractions of 200 rad given daily) for comparison. In each case, normal connective tissue tolerance ($R_f \approx 1800$) was taken as the end point.

The same results are expressed in a different way in Table III, which shows the number of

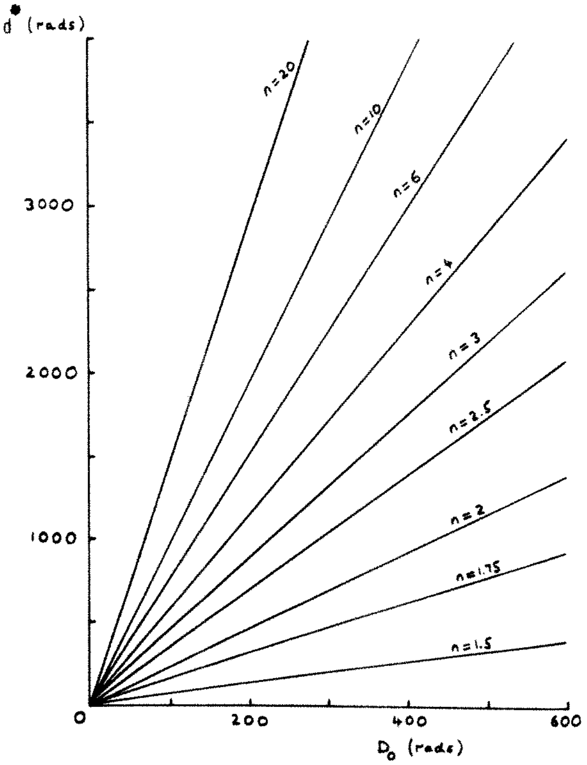

FIG. 3.

Relationship between the optimal dose per fraction, d^* (rad), and the mean lethal dose, D_0 (rad), for various values of the extrapolation number, n.

TABLE I

CHARACTERISTICS OF OPTIMAL SCHEDULES FOR TUMOURS With $n=2$, $D_0=150$ and various doubling times

Doubling time days	Dose/ fraction rad	Time between fractions days	Total no. of fractions	Total time days
10	350	4	16	58
30	350	11	19	200
50	350	18	21	380
70	350	25	22	550
90	350	32	23	740
110	350	39	23	910
130	350	47	24	1,120

N.B. All non-integer quantities have been rounded in the above table.

TABLE II

COMPARISON OF A CONVENTIONAL SCHEDULE WITH A NUMBER OF OPTIMAL SCHEDULES FOR TUMOURS
With $n=2$, $D_0=150$ and various doubling times

Doubling time days	Conventional schedule: Fractional cell survival at completion of schedule ($R_f \approx 1800$)	Optimal schedule: Fractional cell survival at completion of schedule ($R_f \approx 1800$)
10	$5{\cdot}5 \times 10^{-10}$	$7{\cdot}0 \times 10^{-11}$
30	$1{\cdot}5 \times 10^{-10}$	$1{\cdot}0 \times 10^{-11}$
50	$1{\cdot}0 \times 10^{-10}$	$6{\cdot}2 \times 10^{-13}$
70	$9{\cdot}0 \times 10^{-11}$	$1{\cdot}4 \times 10^{-14}$
90	$8{\cdot}4 \times 10^{-11}$	$3{\cdot}0 \times 10^{-15}$
110	$8{\cdot}2 \times 10^{-11}$	$3{\cdot}0 \times 10^{-15}$
130	$7{\cdot}8 \times 10^{-11}$	$4{\cdot}0 \times 10^{-16}$

fractions which would have to be given in order to achieve the same tumour cell kill as each optimal schedule in turn. As may be seen from the R_f values, the conventional schedule would have to be continued well beyond tissue tolerance in order to equal the tumour-cell kill of the optimal schedule in almost every case.

It is noteworthy that the optimal schedules are very much more protracted than conventional schedules, that the superiority of the optimal schedules increases with volume doubling time and that this superiority is unlikely to be significant for tumours whose doubling times are of the order of a week or less. Optimal schedules do not therefore hold much promise for fast growing tumours, which would be almost as well treated conventionally.

All the preceding discussion applies to tumours with "typical" survival curve parameters ($n \approx 2$, $D_0 \approx 150$). As Ellis has recently pointed out (Ellis, 1974), a possibly important, though somewhat untypical, case is that of tumours whose cells have a survival curve giving very high extrapolation numbers. A number of such cases have been reported (Reinhold, 1966; Van Putten, 1968; Hewitt, 1967; Dewey, 1971) and consist of tumour types usually classified as "radio-resistant" when treated by conventional schedules.

Assuming a "typical" doubling time of 70 days (Tubiana, 1971) we have computed optimal schedules and their effects for several such tumours (Wheldon and Kirk, 1975). The results of the computation are given in Table IV which shows the striking superiority of the optimal schedules which, in agreement with Ellis' earlier suggestion (Ellis, 1974), consist of a small number of large doses very widely spaced apart. Conventional schedules would be expected to treat such tumours remarkably poorly.

TABLE III

Comparison between various optimal schedules and a conventional optimal schedule continued beyond tissue tolerance to reach the same surviving fraction

Doubling time	Conventional schedule			Optimal schedule
days	No. of (daily) fractions	Total dose rad	Normal tissue effect (R_f)	Normal tissue effect (R_f)
10	30	6,000	1,825	1,850
30	36	7,200	2,050	1,840
50	40	8,000	2,200	1,850
70	42	8,400	2,270	1,840
90	43	8,600	2,300	1,840
110	44	8,800	2,340	1,800
130	46	9,200	2,400	1,820

Of course, it is perhaps arguable whether the CRE system can be extrapolated to deal with such unusual schedules. Moreover, the assumed doubling time is a guess, and may in any case shorten as the tumour regresses.

Nevertheless, the large magnitude of the difference between the optimal and conventional schedules provides encouragement, and the radiotherapy of tumour cells with high n-values should be capable of substantial improvement.

A further point of interest concerns the sensitivity of the optimum to small changes in the dose per fraction and the inter-fraction interval. Optimal therapy is unlikely to be of practical use if small errors in the estimation of the parameter values lead to the derivation of a schedule whose effect is very much worse than optimal.

To investigate this we again take $n=2$ and $D_0=150$, fix τ at 70 days and compute the final tumour cell population for values of d and t on either side of the true optimum. Figures 4 and 5, respectively, illustrate the criticality of choice of dose and of interval. In both diagrams the broken lines indicate the survival level achieved by a conventional schedule.

The second diagram shows a steeper descent to the minimum than the first; however, in neither case is the descent so steep as to make absolute precision a necessity. Some margin of error therefore is indicated in the estimation of the parameter values which determine d and t.

TABLE IV

Comparison of optimal and conventional schedules for radio-resistant tumours with high extrapolation number

Tumour	Conventional schedule	Conventional surviving fraction	Optimal schedule	Optimal surviving fraction
Osteosarcoma, rhabdomyosarcoma $n=10$ $D_0=120$	$d=200$ rad $T=1$ day 30 fractions	$2{\cdot}8\times10^{-2}$	$d=1{,}150$ rad $T=110$ days 4·4 fractions	$1{\cdot}33\times10^{-12}$
Melanoma $n=25$ $D_0=85$	$d=200$ rad $T=1$ day 30 fractions	$1{\cdot}1\times10^{-1}$	$d=1{,}200$ rad $T=165$ days 4·4 fractions	$2{\cdot}19\times10^{-19}$

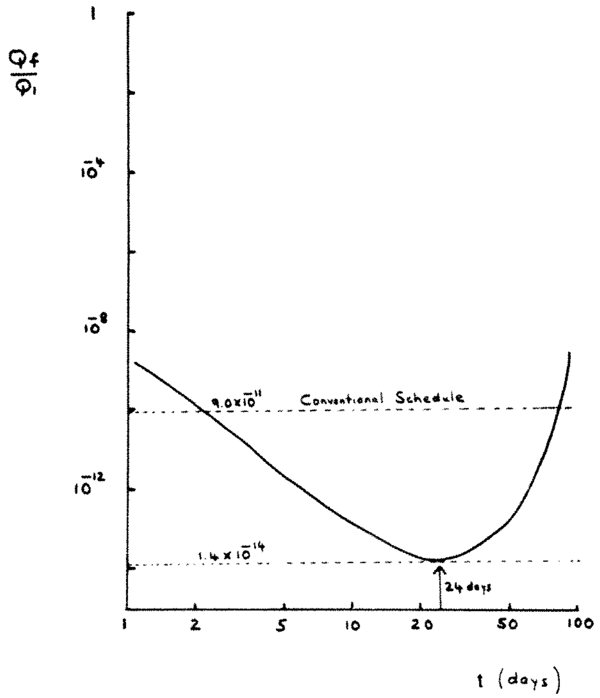

FIG. 4.

Graph of the variation of surviving fraction of tumour cells, Q_f/Q_0, with time-interval (t) between fractions when the dose per fraction (d) is held constant at the optimal value. Parameters: $\tau=70$ days, $d=350$ rad, $n=2$, $D_0=150$, $R_f=1{,}760$, $a=0{\cdot}65$, $b=0{\cdot}11$.

The surviving fraction from a "conventional schedule" (30 fractions of 200 rad daily) is also shown.

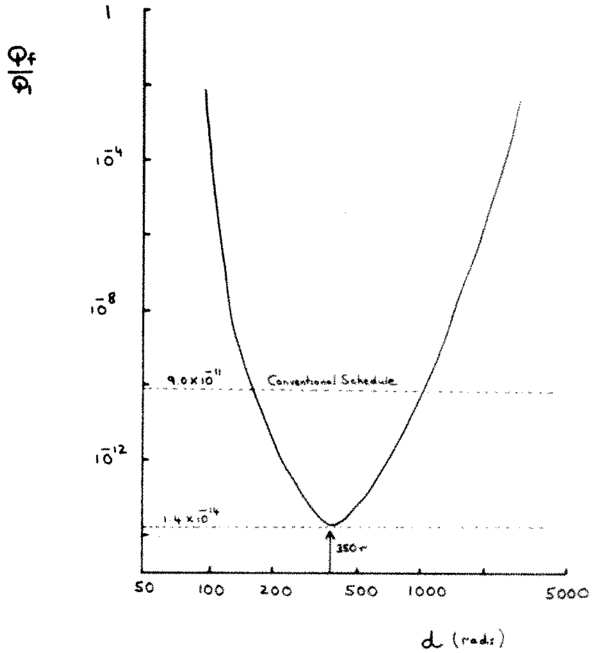

FIG. 5.

Graph of the variation of surviving fraction of tumour cells, Q_f/Q_0, with dose per fraction when the time interval, t, between treatments is held constant at the optimal value. Parameters: $\tau=70$ days, $t=24$ days, $n=2$, $D_0=150$, $R_f=1{,}760$, $a=0{\cdot}65$, $b=0{\cdot}11$.

The surviving fraction from a "conventional schedule" (30 fractions of 200 rad daily) is also shown.

EXTENSION OF THE ANALYSIS TO MORE REALISTIC MODELS

The main purpose of the present analysis is to lay the groundwork for the more complex analysis of more realistic models. The present model is over-simplified in a number of respects.

Few tumours grow in purely exponential fashion. Gompertzian growth appears to be more common (Mendelsohn, 1963; Laird, 1964, 1965; Steel and Lamerton, 1966; Salmon 1971; Bichel, 1971). However, even Gompertzian growth need not be followed. There are theoretical reasons for believing that some neoplasms (*e.g.* acute leukaemia) may follow a stochastic growth law which cannot be easily reconciled with any simple deterministic growth curve at all (Wheldon, 1975).

In addition, it is quite probable that either the ratio of hypoxic to well-oxygenated cells or the ratio of cycling to out-of-cycle cells, or both, will change during therapy, giving rise to an apparent evolution in the radiobiological properties of the tumour cell population as a whole.

Finally, more patients presently die of metastatic disease than of their primary neoplasm. If very protracted schedules are to be introduced, it will be necessary to make some assessment of the likelihood of dissemination beyond the treated volume occurring during treatment.

Each of these problems will be tackled in forthcoming papers. The key observation to the extension of the present analysis is the non-appearance of the CRE radiation damage index R_f in equations (12) and (13). The implication of this is that an optimal schedule intended to stop well short of tolerance is identical in structure to an optimal schedule which goes all the way to tolerance (*i.e.* a tolerance schedule may be regarded as the sum of a number of subtolerance schedules).

This observation allows us to handle the problem of tumours whose properties change as treatment proceeds. If we consider the case of a tumour following a Gompertzian growth curve, which is slow-growing when large and fast-growing when small, it is not difficult to see that the radiation fractions should be spaced well apart at the beginning of treatment but should come closer together as treatment proceeds. Provided the Gompertzian parameters can be estimated (Lloyd, 1975) non-uniform optimal schedules can be designed by regarding the tumour as exponentially growing at any instant but with different doubling times over different intervals.

This approach, and similar approaches to some of the other problems mentioned, will be presented in detail in later papers. As predicted by Fowler (1968), optimal radiotherapy may well turn out to consist of a multi-phasic regime of treatment schedules, one phase giving way to another as the tumour size decreases, its cellular composition alters and the balance of competing factors changes.

Conclusions

Several conclusions can be drawn from this preliminary study.

1. For an exponentially growing tumour the optimal inter-fraction interval is directly proportional to the volume doubling-time of the tumour, and the optimal dose per fraction is directly proportional to the D_0 value of the tumour cell-survival curve. Both optimal interval and optimal dose increase non-linearly with survival curve extrapolation number (n).

2. The structure of an optimal schedule (*i.e.* the interfraction interval and the optimal dose per fraction) is not affected by the level of normal tissue damage (as measured by R_f) at which the schedule is terminated. This controls only the total number of fractions to be given.

3. Preliminary calculations based on sparse data suggest that optimal schedules should be significantly better than those in current use. The superiority of optimal schedules increases with the doubling time of the tumour and the extrapolation number of the survival curve.

Acknowledgments

We are grateful to Mrs. Elizabeth Wheldon and to Dr. John Usher (Department of Mathematics, Glasgow College of Technology) for their helpful comments on the analysis.

REFERENCES

Alper, T. (Ed.), 1975. Cell survival after low doses of radiation (John Wiley and Institute of Physics, London).

Bellman, R., 1957. *Dynamic Programming* (Princeton University Press, Princeton, New Jersey).

Berry, R. J., Wiernik, G., Patterson, T. J. S., and Hopewell, J. W., 1974. Excess late subcutaneous fibrosis after irradiation of pig skin, consequent upon the application of the NSD formula. *British Journal of Radiology*, *47*, 277–281.

Bichel, P., 1971. Feedback regulation of the growth of ascites tumours in parabiotic mice. *Nature*, *231*, 449–450.

Cohen, L. H., 1973. Cell population kinetics in radiation therapy: optimization of tumour dosage. *Cancer*, *32*, 236–244.

Dewey, D. L., 1971. The radiosensitivity of malignant melanoma cells in culture. *British Journal of Radiology*, *44*, 816–817.

Elkind, M. M., and Whitmore, G. F., 1967. *The radiobiology of cultured mammalian cells.* (Gordon and Breach, New York).

Ellis, F., 1969. Dose, time and fractionation: a clinical hypothesis. *Clinical Radiology*, *20*, 1–7.

1971. Nominal standard dose and the ret. *British Journal of Radiology*, *44*, 101–108.

1974. The NSD concept and radioresistant tumours. *British Journal of Radiology*, *47*, 909.

Fischer, J. J., 1971. A mathematical simulation of the radiation therapy of solid tumours. *Acta Radiologica (Therapy, Physics and Biology)*, *10*, 73–85.

Fowler, J., 1966. Radiation biology as applied to radiotherapy. In *Current topics in radiation research*, edited by M. Ebert and A. Howard, Vol. II (North Holland Publishing Co., Amsterdam).

1968. The rationale of dose fractionation. In *Frontiers of radiation therapy and oncology*, edited by J. M. Vaeth Vol. 3 (S. Kerger, New York).

Hethcote, H. W., and Waltman, 1973. Theoretical determination of optimal treatment schedules for radiation therapy. *Radiation Research*, *56*, 150–161.

Hewitt, H. B., 1967. *Cellular radiosensitivity and the volume of response of tumours to irradiation.* Proceedings Conference on Radiation Biology and Cancer, pp. 9–16 (Radiological Society of Japan, Kyoto, Japan).

Kirk, J., 1976. *The cumulative radiation effect* (Livingstone Press, Edinburgh) (in press).

Kirk, J., Gray, W. M., and Watson, E. R., 1971. Cumulative radiation effect: Part I—Fractionated treatment regimes. *Clinical Radiology*, *22*, 145–155.

Kirk, J., Cain, O. S., and Gray, W. M., 1976. Cumulative radiation effect: Part VI—Computational aspects. *Clinical Radiology* (in press).

Laird, A. K., 1964. Dynamics of tumour growth. *British Journal of Cancer*, *18*, 490–502.

1965. Dynamics of tumour growth: comparison of growth rates and extrapolation of growth curve to one cell. *British Journal of Cancer*, *19*, 278–291

Liversage, W. E., 1971. A general formula for equating protracted and acute régimes of radiation. *British Journal of Radiology*, *42*, 432–440.

Lloyd, H. H., 1975. Estimation of tumour cell kill from Gompertz growth curves. *Cancer Chemotherapy Reports*, *pt. 1*, *59*, 267–277.

Mendelsohn, M. L., 1963. Cell proliferation and tumour growth. In *Cell Proliferation*, edited by L. F. Hammerton and R. J. M. Fry (Blackwell, Oxford).

Orr, J. S., 1974. The NSD formula. *British Journal of Radiology*, *47*, 824.

Orton, C. G., 1975. The NSD formula and the Oxford pig skin experiments. *British Journal of Radiology*, *48*, 67–68.

Orton, C. G., and Ellis, F., 1974. A simplification of the use of the NSD formula in practical radiotherapy. *British Journal of Radiology*, *46*, 529–537.

Reinhold, H. S., 1966. Quantitative evaluation of the radiosensitivity of cells of a transplantable rhabdomyosarcoma in the rat. *European Journal of Cancer*, *2*, 23–42.

Salmon, S. E., 1971. Immunoglobin synthesis and the natural history of multiple myeloma. *British Medical Journal*, *2*, 321.

Steel, G. G., and Lamerton, L. F., 1966. The growth rate of human tumours. *British Journal of Cancer*, *20*, 74–86.

STEWARD, P. G., and HAHN, G. M., 1971. The application of age response functions to the optimization of treatment schedules. *Cell and Tissue Kinetics*, *4*, 279–291.

TUBIANA, M., 1971. Kinetics of tumour cell proliferation and radiotherapy. *British Journal of Radiology*, *44*, 325–347.

TURRESSON, I., and NOTTER, G., 1975. Skin reactions after different fractionation schedules giving the same cumulative radiation effect. *Acta Radiologica (Therapy, Physics, Biology)*, *14*, 475–484.

VAN PUTTON, L. M., 1968. Tumour oxygenation during fractionated radiotherapy; studies with a transplantable mouse osteosarcoma. *European Journal of Cancer*, *4*, 173–182.

WHELDON, T. E., 1975. Mitotic autoregulation of normal and abnormal cells: alternative mechanisms for derangement of growth control. *Journal of Theoretical Biology*, *53*, 421–433.

WHELDON, T. E., and KIRK, J., 1975. Optimal radiotherapy of radioresistant tumours. *British Journal of Radiology*, *48*, 870–871.

WHITMORE, G. F., and TILL, J., 1964. Quantitation of cellular radiobiological responses. *Annual Reviews of Nuclear Science*, *14*, 347–374.

Book reviews

Radiobiology Examination Review Book. By T. Prempree, A. M. El-Mahdi, J Shaeffer and S. C. Barranco, pp. 128, 1975 (Flushing, N.Y., Medical Examination Publishing Co.), $7.50.

The authors state that "the primary purpose of this book is to serve as an aid to radiology residents in their preparation for the American Board of Radiology examinations" and secondarily that it will "help the student to identify specific areas of weakness in this multi-disciplinary field". The range of subjects of the 900 multiple choice questions is such that the latter rather negative purpose may well be fulfilled and to this extent may be of some help to students taking English rather than American examinations.

It is, however, a type of book which, despite the authors' wishes, will encourage acceptance by the students of a rather superficial acquaintance with some of the facts of radiobiology rather than an understanding of the fundamental principles involved. Many examples could be chosen of questions which foster this approach; one must suffice. No. 22 states "the compensatory wave of mitosis induced by irradiation of a biological system is the result of: A. release of blocked G_2 phase cells, B. a loss of reproductive integrity, C. interphase death, D. all of the above, E. none of the above." The answer given as correct, is A. Whilst there may be a G_2 phase block induced for a limited time by irradiation and which is followed by a wave of mitosis above the normal level, how, it may be asked, is this "compensatory" and for what? The damage to the reproductive integrity of some cells in a tissue and the death of others in interphase does lead to compensatory proliferation amongst survivors in a tissue in which a "steady state" is normally maintained; yet answers B and C are said to be wrong. The "biological system" referred to in the question is not in any way defined, and so the whole question becomes superficial and misleading.

Other questions which involve a simple knowledge of fact are straightforward.

Whether or not students like this type of approach to learning is a matter of individual taste; but in the reviewer's opinion, except where the examination is composed of similar multiple choice questions, a book of this nature is likely to be harmful rather than helpful.

R. H. THOMLINSON.

Cancer Mortality, England and Wales 1911–1970. Studies on Medical and Population Subjects No. 29, pp. 64, 1975 (London, H.M.S.O.), £5·25 paperback.

In 1957 the General Registry Office published a summary of statistics relating to cancer mortality and survival (McKenzie, Case and Pearson, 1957). This new volume extends most of the tables in the original publication up to 1970.

The first two tables detail number of deaths and the mortality rates for "all neoplasms" and "all malignant neoplasms"; the next 32 tables are concerned with systemic cancers and the two final tables cover "Hodgkin's disease and leukaemia". Each table lists both the number of deaths and mortality rates for five-year age groups in successive five-year calendar periods; all rates are expressed as deaths per million person-years at risk. The calendar years covered vary depending on the changes that have been made in disease classification—the list of such changes being given in an Appendix. A brief indication is given of the trend of the mortality figures.

These tables should prove to be useful to all oncologists as a source of information of the changes that have occurred in cancer mortality at different ages in this century.

T. J. DEELEY.

REFERENCE

MCKENZIE, A., CASE, R. A. M., and PEARSON, J. T., 1957. *Cancer Statistics for England and Wales 1901–1955: a summary of data relating to mortality and morbidity*. General Register Office. Studies on Medical and Population Subjects. (London *H.M.S.O.* (out of print)).

1976, *British Journal of Radiology*, *49*, 450–457

Pseudo optimization of radiotherapy treatment planning*

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(*Received February, 1975 and in revised form December, 1975*)

ABSTRACT

A chain consisting of three computer programs has been developed for treatment planning of external beam radiotherapy without manual intervention. Apart from the data necessary to identify the patient, the institute, etc., the input consists only of the anatomical information indicated on an outline sheet.

Firstly, combinations of incidence directions for a two or three-beam set-up are judged by the first program. Then a limited number of these combinations is selected by this program. For every beam of each selected combination a set of wedges and weights is calculated. Next the dose distributions belonging to each combination with wedges and weights are judged by the second program. Finally, the isodose pattern of the dose distribution judged the best is determined by the third program.

The judgement of incidence directions is done by coarse score functions corresponding to a set of criteria. The judgement of dose distributions is done by detailed score functions corresponding to another set of criteria. These criteria with their score functions are treated in some detail. The use of the programs in the clinic is discussed and results are shown.

Radiotherapists and physicists would be relieved from a great deal of tedious treatment planning and could devote more attention to other aspects of radiotherapy if a computer program existed which did on its own all the routine planning for external beam treatment. We have developed a chain of programs for the planning of radiotherapy treatment with megavoltage X or γ rays. Apart from the data necessary to identify the patient, the institute, etc., the input consists only of the anatomical information registered on the outline sheet.

For the evaluation of incidence directions and the judgement of dose distributions we use different sets of score functions. As early as 1967 the judgement of dose distributions using score functions was done by Hope and Orr (1965) and by Hope *et al.* (1967). Some of their score functions have been used although modified. However, our way of reaching the final score is essentially different. In our case the final score consists of a weighted sum of the score-function values instead of a weighted sum of powers of score-function values.

Early approaches, in which the program was free to select incidence directions as well as weights, were made by Gallagher (1967) and Bahr *et al.* (1968). They used the method of linear programming for the optimization of treatment planning. The same technique was also used by Jameson and Trevelyan (1969) to optimize pelvis treatments with a pelvic wedge. More details about these approaches are given by Wood (1974).

An outline of our programs, together with their input, will be given, and the criteria with their corresponding score functions will be treated in some detail. The program for the calculation of dose distributions is similar in performance to programs published by others (Bahr *et al.*, 1968; Stirling, *et al.*, 1964; Mauderli and Fitzgerald, 1965; Van de Geyn, 1965; Allewaert, 1972) and therefore will not be explained. The daily routine use will be discussed, and results will be shown.

METHODS

The method of obtaining an optimized treatment plan can be divided into four stages:

(1) selecting a number of appropriate combinations of incidence directions for the beams;
(2) determining suitable wedge filters and weights for each beam of a combination;
(3) selecting the final plan out of the plans corresponding to the above mentioned combinations of incidence directions with their wedges and weights;
(4) calculating the dose distribution of the final plan.

Combinations of incidence directions are selected by evaluating them with a set of coarse score functions based on beam-incidence criteria. The coarseness of the score functions increases the speed of calculation, and is required because of the large number of possible combinations. Wedge-filters are determined by calculating the angle over which the isodoses of each plain beam have to rotate in order to be angled at 180 deg. to each other (two beams) or at 120 deg. to each other (three beams) (see also Fig. 3A and B). For every beam of each combination a series of weights is provided. Treatment plans are judged with a set of detailed score functions based on dose-distribution criteria. These score functions use dose values, calculated at points inside and outside the target area, and around vulnerable regions. In order to distinguish between these two sets of score functions, the score functions based on beam-incidence criteria will be called the coarse score functions, while the score functions based on dose-distribution criteria will be called the detailed score functions.

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*Part of this paper was presented at the 3rd Congress of the European Association of Radiology, Edinburgh, 1975, June 22–27.

Outline of the programs

The program chain consists of three programs:

(1) MFSEARCH, a program that, by means of coarse score functions, assigns a score value to all combinations of incidence directions for two or three beams. Based on these score values it then selects a number (*e.g.* six) of combinations of incidence directions. Finally a set of wedges and weights is calculated for every beam of a selected combination of incidence directions.

(2) MFOPTIM, a program that, by means of detailed score functions, judges each of the dose distributions determined by the setting of the beams obtained by MFSEARCH. On the basis of this judgement it selects the best of these dose distributions.

(3) MF3DEXT, a program that calculates the dose distribution selected by MFOPTIM and prints this distribution on a line printer or plots it on a plotter.

A flowchart of these programs is given in Fig. 1. The programs have been written in ALGOL-60, using 40 K words central memory on a Control Data Cyber 73 computer.

Input of patient data

The entering of data necessary to identify the patient, the institute, etc. will not be discussed. The description of the contour and the target area is done by providing the lengths of the radii drawn at regular intervals from a chosen centre of the target area (see Discussion) to the patient contour and to the target contour (Fig. 2). In the same way the contour of each vulnerable region is described with radii drawn from a centre chosen inside the region. Furthermore, the positions of these centres relative to the target centre and the permissible dose in each of these regions relative to the mean dose in the target area are given.

Upperbounds for the values of some score functions are given to the programs in order to save computational time by immediately rejecting dose distributions exceeding one of these upperbounds. The program chain is also provided with those beam-incidence directions which are impossible or unwanted.

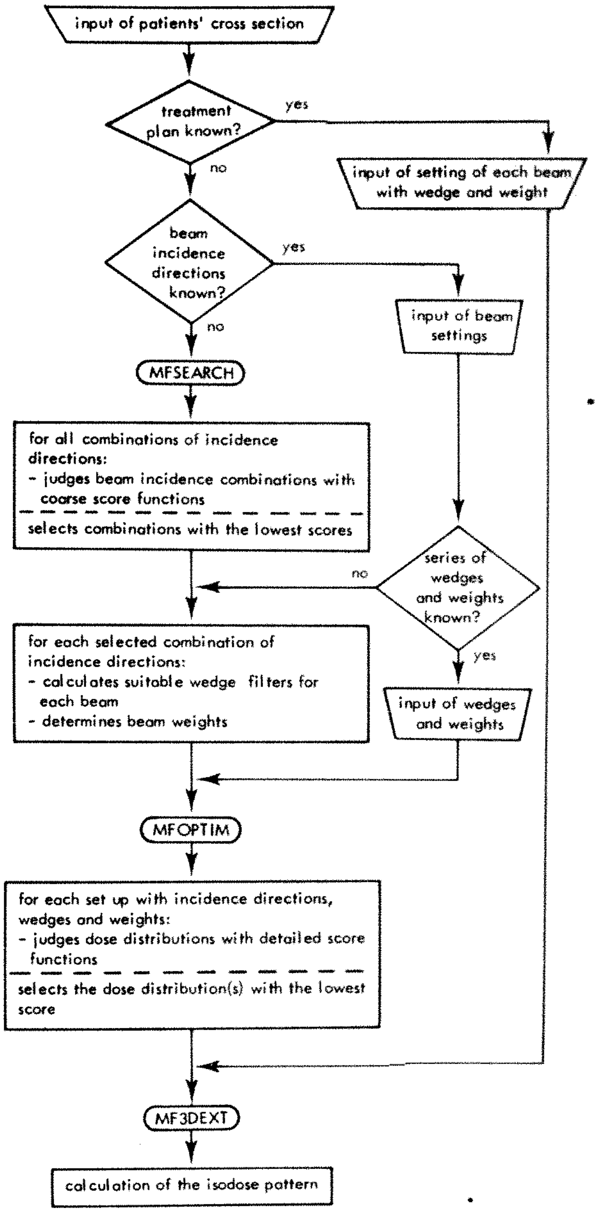
input of patients' cross section
treatment plan known?
yes
no
input of setting of each beam with wedge and weight
beam incidence directions known?
yes
no
input of beam settings
MFSEARCH
for all combinations of incidence directions:
- judges beam incidence combinations with coarse score functions
selects combinations with the lowest scores
series of wedges and weights known?
no
yes
for each selected combination of incidence directions:
- calculates suitable wedge filters for each beam
- determines beam weights
input of wedges and weights
MFOPTIM
for each set up with incidence directions, wedges and weights:
- judges dose distributions with detailed score functions
selects the dose distribution(s) with the lowest score
MF3DEXT
calculation of the isodose pattern

Fig. 1.

Flow-chart of the program chain.

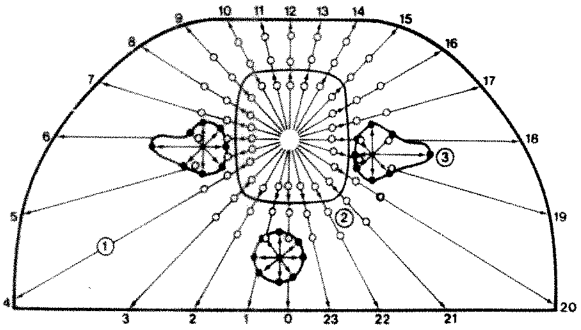

Fig. 2.

Description of the patient cross-section and the position of the points in which the dose delivery is calculated:

(1) radii to describe the contour of the cross-section, target area and vulnerable regions,

(2) sample points inside and outside the target area,

(3) sample points on the contour of the vulnerable regions.

Judgement of incidence directions

For the judgement of incidence directions MFSEARCH uses coarse score functions based on the following six criteria:

(1) dose delivery to tumour relative to incidence dose;

(2) equality of dose delivery to target area;

(3) dose delivery to vulnerable regions;

(4) integral absorbed dose;

(5) obliqueness of the beam entries to the patient contour;

(6) mutual beam positions.

To each criterion a score function is attached. The deviation of the function value from zero indicates the deviation from the ideal case. For discussion of these score functions, the case of two beams (i and j) will be treated in the next part of this section.

1. Dose delivery to tumour relative to incident dose:
$EXT = EXTTRM_i + EXTTRM_j$ with $EXTTRM =$
$1\text{-}\exp(-\mu r)$
r is the distance measured along the central axis of the beam from the skin to the target centre. μ is the effective linear absorption coefficient of the beams in tissue. The fraction of the depth dose left after traversing a distance r in tissue is taken as $\exp(-\mu r)$. The fraction of the depth dose absorbed after traversing r, the absorbed fraction, is then: $1\text{-}\exp(-\mu r)$. This rough approximation with which the beam absorption in tissue is described, has been shown to be sufficient for the judgement of combinations of incidence directions.

The score function EXT has been designed such that for all acceptable cases its value is less than 1. A value greater than 1 means that the tumour dose $\{\exp(-\mu r_i) + \exp(-\mu r_j)\}$ is smaller than both of the incident doses (each with the value 1).

2. Equality of dose delivery to target area:
$EQUAL = 2\{1 - \exp(-\mu . |r_i - r_j|)\}$.
This function becomes 0 when $r_i = r_j$ and 1 when the absorbed fraction is 0·5 over a distance $|r_i - r_j|$.

3. Dose to vulnerable regions:
$CRIT = CRITTRM_i + CRITTRM_j$ with $CRITTRM$ being the summation over all vulnerable regions of $f.\exp(-\mu d)/D_p$. d is the distance from the skin to the centre of the vulnerable region, parallel to the central axis of the beam. D_p is the permissible dose in the vulnerable region expressed as a fraction of the mean dose in the target area. The coefficient f accounts for the distance of the centre of the vulnerable region in question from the beam. $f = 1$ when the beam goes through the vulnerable region; we chose $f = 0{\cdot}2$ when the beam misses the vulnerable region at a distance less than 5 mm and $f = 0$ when this distance is more than 5 mm. Because of its structure $CRIT$ is a score function which can exceed the value 1 in acceptable combinations of incidence directions.

4. Integral absorbed dose:
$FLD = FLDTRM_i + FLDTRM_j$ with
$FLDTRM_k = (FIELD_k - FIELD_{min})/6$.
For every incidence direction k the corresponding field size ($FIELD_k$) is determined as the smallest diameter, rounded off to 0·5 cm, which encompasses the target area. $FIELD_{min}$ is the minimum value of all field sizes $FIELD_k$. When $FLDTRM_k = 1$, $FIELD_k$ and $FIELD_{min}$ differ by 6 cm. This value of 6 was arbitrarily chosen and is not essential, because in the expression for the total score FLD is multiplied by a weighting factor. The score function FLD favours small beams above broad beams and in this way influences the integral absorbed dose.

5. Obliqueness of the beam entries to the patient contour:
$CURV = CURVTRM_i + CURVTRM_j$ with
$CURVTRM = 0{\cdot}6 \tan(\phi)$.
ϕ is the angle of the central axis of the beam with the perpendicular to the contour at the point of intersection of the central axis with the contour. ϕ is often called the "angle of incidence". $CURVTRM = 1$ for $\phi = 60$ deg; the factor 0·6 is also chosen arbitrarily (see 4).

6. Mutual beam positions:

$$INV = \left| \frac{4(j-i)}{rn} - 1 \right|, j > i, j - i \leq rn/2.$$

rn is the number of radii used to describe the patient contour and the target area. The restrictions for i and j prevent combinations of incidence directions being evaluated more than once. See Fig. 2 for the meaning of the numerical value of i and j. When the radii are drawn at every 15 deg., $rn = 360/15 = 24$. In this case, when two beams are perpendicular to each other, $j - i = 6$ and consequently $INV = 0$. When two beams are opposing or coincide, $j - i = 12$ or 0 and in both cases $INV = 1$.

In the case of three beams i, j and k, the score functions EXT, $CRIT$, FLD and $CURV$ are constructed in the same way: adding the separate beam contributions. To keep the function value in the same range as in the case of two beams, the beam contributions are multiplied by 2/3. For example:
$EXT = \frac{2}{3}(EXTTRM_i + EXTTRM_j + EXTTRM_k)$.

$EQUAL$ and INV are constructed slightly differently:

$$EQUAL = 2\left[1 - \exp\left\{-\frac{\mu}{3}\left(\left|r_i - r_j\right| + \left|r_j - r_k\right| + \left|r_i - r_k\right|\right\}\right)\right]$$

$$INV = \tfrac{1}{2}\left\{\left|\frac{3(j-i)}{rn} - 1\right| + \left|\frac{3(k-j)}{rn} - 1\right|\right\}, i < j < k.$$

The construction of the score function INV is such that the value 0 is obtained when the beams make an angle of 120 deg. with each other; the value 1 is obtained when the angle between i and j and between j and k is either 0 deg. or 240 deg.

The total score consists of a weighted sum of the different score functions. At the present time good

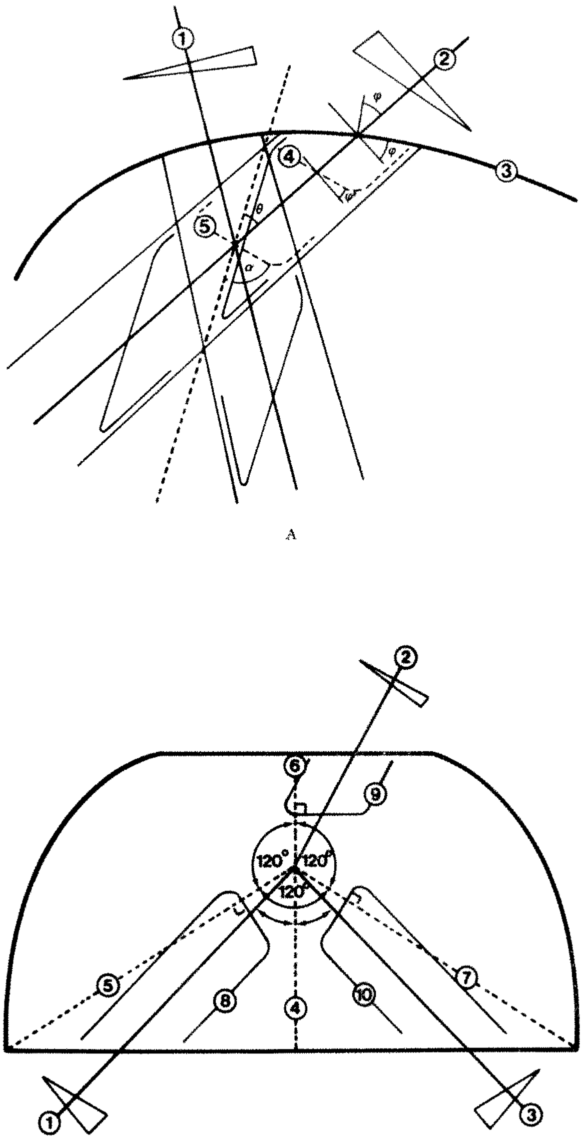

FIG. 3.

Calculation of wedge-filter angle.

(A) Combination of two beams.

1,2: central axes of the beams.
3: outline of the patient.
4,5: isodose lines obtained when the wedge-filter is not inserted into the beam.
ϕ: angle of central axis with perpendicular to the skin.
ϕ': angle of isodose lines 4,5 with perpendicular to the central axis.
θ: angle between the bisector of the central axes and either one of these axes.
α: angle (in degrees) between the isodose lines 4,5 and the bisector of the central axes.

(B) Combination of three beams.

1,2,3: central axes of the beams.
4: bisector of axis 1 and axis 3.
5,6,7: perpendiculars to the isodose lines:
8,9,10: of the respective beams.

results are obtained with the following weighting values:

$$SCORE = 2.EXT + 2.EQUAL + 1.CRIT + 1.FLD + 1.CURV + 2.g.INV.$$

When the distance of the chosen target centre to the skin is less than or about the depth at which electronic equilibrium is reached (with 8 MV X rays 2 cm) $g=0$, otherwise $g=1$. The case with $g=0$ will hereafter be called a plan with a superficially lying target (See Fig. 5). This elimination of *INV* from the score is necessary because the dose delivered increases very rapidly just under the skin and then remains rather constant over some distance (2 cm for 8 MeV X rays). Wedge-filters and angles between incidence directions are then of little importance in achieving good treatment plans.

A combination of incidence directions is immediately rejected when one of the following maximum values is exceeded:

$$EXT: 1.2, EQUAL: 1, CRIT: 1, CURV: 1.$$

Wedge-filters and weights

Once the (*e.g.* six) best combinations of incidence directions are selected, wedge-filters and weights are determined for each beam of such a combination.

In the case of two beams, wedge-filters are inserted in each of the beams such that the isodose lines are parallel to the bisector of the angle between both beams. Thus the isodose lines have to rotate: $\alpha = 90 - \theta + \phi'$ deg. (Fig. 3A).

The treatment set up only gives the angles of incidence (ϕ) and the angle between the beams (2θ). This means that the influence of oblique incidence (ϕ) on the angle of the isodose lines with the central axis (ϕ') must be expressed. It can be shown that $\tan(\phi') = 0{\cdot}6 \tan(\phi)$ for 8 MV X rays and 100 cm focus-target centre distance. For ^{60}Co and 80 cm source-target centre distance $\tan(\phi') = 0{\cdot}7 \tan(\phi)$, both factors depending somewhat on the field sizes.

The value of θ is derived from the incidence directions of the two beams and is the same for both beams. It turns out to be sufficient, even in the case of oblique incidence, to insert in each of the beams a wedge-filter with a wedge angle of $90 - \theta + \phi'$ deg. A wedge-filter with a wedge angle of α degrees is a wedge-filter which, in the case of normal incidence of the beam to the skin, will turn the isodose lines of this beam through an angle of α deg. A plain field is considered as due to a wedge-filter with an angle of 0 deg. Because of the rough approximations in the derivation of the wedge angle and because of the limited number of wedge-filters available, three wedges are selected for each beam with their wedge angles near $90 - \theta + \phi'$ deg. The program reduces the number of wedges to two if three wedges are not available. In the case of three beams, a wedge is inserted in each beam such that the isodose lines of each beam make an angle of 120 deg. with the isodose lines of the other beams (Fig. 3B). The determination of suitable wedge-filters is analogous to the case of two beams. Usually two wedges are determined for each beam.

In the case of a superficial-lying target, only the oblique incidence of a beam is compensated; thus a wedge-filter with a wedge angle ϕ' is inserted in each beam (Fig. 5). The reason for this has already been discussed.

As will be explained in the next section, the program for judgement of dose distributions, MFOPTIM, has been written such that changing weights for the beams and rejudging the modified dose distributions uses very little computer time. Therefore less effort has been spent on programming the calculation of weights. In the case of two beams we gave, when $r_i < r_j$, beam j a weight 1 and beam i a series of weights, *e.g.* 0·6, 0·7 . . ., 1·6. In the case of three beams, when $r_i < r_k$ and $r_j < r_k$, beam k gets weight 1 and beam i and j both get a series of weights, *e.g.* 0·4, 0·6, . . ., 2·0.

To summarize the stage of the planning procedure at this point: MFSEARCH has now determined a number of combinations of incidence directions. Each beam of such a combination is provided with appropriate wedge-filters and weights. For example, with three combinations of incidence directions for a three-field technique, two wedges for each beam and two beams with eight weights, the third beam having Weight 1, MFSEARCH offers to MFOPTIM: 3.2.2.2.8.8.1 = 1,536 different dose distributions to be judged.

Judgement of dose distributions

In order to judge a treatment plan, MFOPTIM follows the following procedure. The radii, drawn from the target centre to the contour of the patient cross-section, are provided with a number of sample points. In the same way the contour of the vulnerable regions is provided with sample points. The position of these points is indicated in Fig. 2.

Next the dose distribution at each of these points is calculated for each beam, with weight 1 and with the wedge-filter assigned to it. The result is stored by the program. The calculation is based on tabulated off-axis/on-axis dose ratios and on a central axis depth-dose function. The latter function takes into account the dose increase from the patient surface to the depth of electronic equilibrium. Because the aim of MFOPTIM is to discriminate between treatment plans, a high accuracy in the dose calculation is not necessary, the computing speed being more important. Oblique incidence of the beams on the patient contour is taken fully into account.

Then, using the appropriate weights of the beams, the total dose at each point is determined. Finally, based on the dose values at all these points, the values of the detailed score functions corresponding to the judgement criteria are calculated. In this way change of weights only means multiplying the stored dose values with these modified weights and rejudging the dose distribution.

These criteria and their corresponding detailed score functions are formulated as follows:

(1) Dose homogeneity in the taget area:
$TDH = (D_{t,\,max} - D_{t,\,min})/D_t$
(2) High-dose zones near the target area:
$HDZ_1 =$ (number of points$_1$ with $D_1 > 0{\cdot}9\ D_t)/N_1$
$HDZ_2 =$ (number of points$_2$ with $D_2 > 0{\cdot}7\ D_t)/N_2$
(3) High dose regions distant from the targer area:
$FDM = D_{in,\,max}/D_t$
(4) Dose to vulnerable regions:
For every vulnerable region is calculated:

$DVLN = \dfrac{D_v}{D_t} \cdot \dfrac{100}{D_p}$ and then all these values are added.

(5) Integral absorbed dose:

$$ID = \frac{100}{D_t}\left\{\sum_{B} W_i . R_i . D_{t,\,i}\right\} \Big/ \left\{a \sum_{N} r_j^2\right\}$$

Explanation of the score functions:

(1) $D_{t,\,max}$ is the maximum dose value of the inner points; *i.e.* points situated on the radii at 0·6 cm inside the target contour.
$D_{t,\,min}$ is the minimum dose value defined in the same way.
D_t is the mean dose value of the inner points.
(2) Points$_1$ are outer points situated on the radii at 0·6 cm outside the target contour with dose values D_1. Points$_2$ are outer points situated on the radii at 2 cm outside the target contour with dose values D_2. When a point lies outside the patient contour, it is neglected.
N_1 is the number of points$_1$, N_2 is the number of points$_2$. Thus HDZ_1 is the number of points$_1$ inside the cross section with a dose higher than 90 per cent of D_t, divided by the total number of points$_1$. HDZ_2 is defined in a similar way.
(3) Far from the target area high dose regions will only occur at the entrance area of the beams at the depth at which electronic equilibrium is reached. In the case of a plain beam at normal incidence, the high-dose region lies around the central axis at this depth. When a wedge filter is inserted into the beam the high dose region is displaced from the central axis. The dose in this region will be called the incident dose. The dose at the depth of electronic equilibrium on the central axis is called the field dose. The weight of a beam and the field dose are linearly related to each other.
$D_{in,\,max}$ is the maximum incident dose found among the incident doses of all beams of the treatment plan.
(4) D_v is the mean dose of all points lying on the contour of the vulnerable region in question.
D_p is the permissible dose of this region expressed as a percentage of D_t.
(5) $\sum_{B}$ means summation over all beams.

W_i is the field width of beam i.
R_i is the length of the central axis of beam i through the patient cross-section.
$D_{f,i}$ is the field dose of beam i.
$\sum_N r_j^2$ is the sum of the squares of all radii from the target centre to the patient contour and a is the angle in degrees between two successive radii.
$\frac{a}{100}\sum_N r_j^2$ is an approximation of the area of the patient cross-section.

The final score consists again of a weighted sum of the different score functions and is characteristic for the dose distribution, independent of the way this distribution is achieved (see discussion for the determination of the weighting factors). Good results are obtained with:

$$\text{score}=2.TDH+10.HDZ_1+10.HDZ_2+1.FDM+3.\Sigma DVLN+1.ID;$$

Σ being the summation over all critical regions.

For *TDH*, *FDM* and the different *DVLN*'s, upperbounds are introduced together with the input of patient data. Plans with a value for one of these detailed score functions higher than the corresponding upperbound are immediately rejected. Often-used values for these upperbounds are: *TDH*: 15 per cent, *FDM*: 80 per cent, the percentages being percentages of the mean target dose. When treating the bladder, the upperbound of the ratio D_v/D_t for the rectum is often 70 per cent, with a permissible dose D_p of 50 per cent. For the spinal cord these values are often taken as 50 per cent and 30 per cent.

CLINICAL USE

MF3DEXT and MFOPTIM have now been in use for more than three years; MFSEARCH for more than one year. In our department most megavoltage treatment plans are determined by these programs (300 plans a year). Exceptions are the plans with two opposing beams on straight surfaces without wedge-filters and the difficult plans, *e.g.* with non-coplanar beams. Two radiographers prepare the input, operate the computer terminal and deliver the final plan to the radiotherapists and the physicist for evaluation. After the final plan has been approved, they fill in the treatment instruction sheet and are present at the first treatment of the patient. This computer system has relieved the treatment planning department from a great deal of routine work.

The programs are run on the Control Data Cyber 73 computer of the Academical Computing Centre in Amsterdam. Use is made of a remote batch terminal, located at 200 metres from the radiotherapy department. A high priority level for our programs is granted, so the time between input to and output from the computer is usually short, about five minutes for two or three treatment plans together in one run. The time elapsed between the presentation of a patient outline to the radiographer and the return to the radiotherapist of the optimized plan is in most cases half a day.

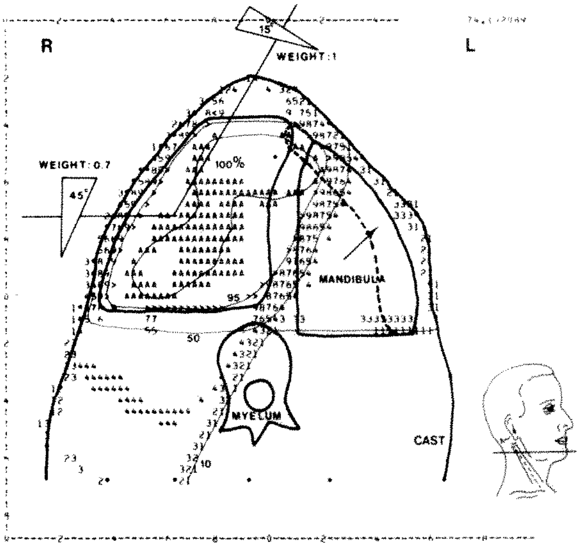

FIG. 4.
Computer-constructed treatment plan (8 MV X) for a tonge—floor of mouth lesion.

Because the programs are batch-processed by the computer, no manual intervention during the running of the programs is possible. Hence much attention was given to the fact that a bad result or no result at all would imply rerunning the programs. For instance, when one or more upperbounds for score function values prevent MFSEARCH or MFOPTIM from obtaining a prefixed minimum number of combinations of incidence directions or of reasonable dose distributions, the program augments the upperbound(s) in question and does the planning again.

All programs of the chain are not necessarily needed for a treatment plan. As indicated in Fig. 1, it is possible to enter the program chain at several levels. For instance, when the incidence directions of the beams are fixed, only a series of suitable wedge-filters and weights has to be determined by MFSEARCH. MFOPTIM and MF3DEXT are then needed to arrive at the final dose distribution.

The maximum number of beams to be handled is three for MFSEARCH and four for MFOPTIM. In both situations the central axis has to lie in the

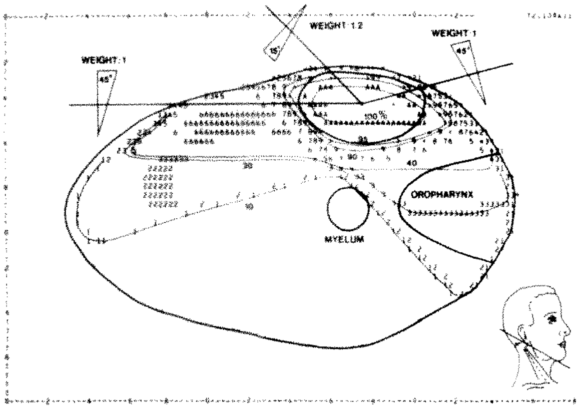

Fig. 5.

Computer-constructed treatment plan (8 MV X) for a superficially lying target area, in this case a glomus tumour. The patient outline is taken from *os mandibularis* to *os occipitalis*.

patient cross-section and must go through the chosen centre of the target area. Until now no need has been felt to change these restrictions.

Examples of the dose distributions achieved by the programs are given in Figs. 4 and 5.

Discussion

A survey of the drawbacks of external beam treatment planning with a computer (—terminal) situated outside the radiotherapy department has been given by Bentley and Milan (1971). It turns out that a considerable disadvantage, especially when more than one run is necessary to achieve a satisfactory result, is the time which elapses between the presentation to and return from the computer of a treatment plan. However, the power of modern large computers, linked with a relatively low-cost terminal, permits the use of extensive chains of programs on a routine basis with possibilities unrealizable with small computers.

Our programs follow a procedure which selects the best plan out of a whole series of reasonable treatment plans including the good and very good ones. There are two reasons for calling this procedure pseudo-optimization of treatment planning. The first reason is that the final plan is selected out of a limited amount (albeit a very large number) of treatment plans. The second reason is that the chosen criteria and the corresponding score functions are only to a certain extent representative of the result of the treatment.

The weighting factors for the score functions of the detailed criteria for the judgement of dose distributions (MFOPTIM) have been determined according to the preferences of our radiotherapists. The question is still open whether one can determine optimum values for all these weighting factors. Reasonably good results can be obtained with quite different sets of weighting factors. The set of weighting factors in use is still being upgraded in the following way.

The radiotherapist, the physicist or the planning radiographer often offers a set of incidence directions with appropriate wedges and weights to MFOPTIM or complete plans to MF3DEXT. A comparison is made between these plans and the corresponding computer-determined plan. In nearly all cases the treatment plan determined by the programs is better or the same. When the reverse is true, much attention is paid to the reason for this misbehaviour of the programs.

Determination of the weighting factors for the criteria of MFSEARCH can be done by means of a mathematical procedure. Each combination of beam incidence directions corresponds to a series of dose distributions because of the different wedges and weights. The values of the coarse score functions for the criteria of MFSEARCH can be linked with the lowest total score value of MFOPTIM for these dose distributions. In this way an equation can be composed with six unknowns (the weighting factors for the coarse score functions of MFSEARCH), with six corresponding coefficients (the values of the single score functions of MFSEARCH) and with the lowest detailed score value of the resulting dose distributions (the best total score determined by MFOPTIM) on the right hand side of the equation. From the plans acquired over more than one year, sets of, *e.g.* 40 equations have been composed and solved by a least-square method. This work is still in progress and eventually will lead to a mathematically-defined set of weightings factors for the score functions of MFSEARCH.

There are certain shortcomings in the score functions used by MFSEARCH and MFOPTIM.

(1) The score function *INV* of MFSEARCH gives the same value for coinciding beams as for opposing beams. It is obvious that the first case is worse than the second one.

(2) The mathematical procedure for the determination of the weighting factors for MFSEARCH often results in a negative factor for *EQUAL*. The reason for this is not fully understood. However, it is clear that, when a beam goes through a vulnerable region, MFOPTIM favours the case of an asymmetrical set up with as little dose delivery by this beam as is permitted by the other score functions.

(3) In the same way it was found that the weighting factor of *CURV* is negative when solving equations composed only of bladder treatment plans. Probably the curvature of the lateral parts of the patient contour influences the dose homogeneity in the target area.

(4) The function *FDM* of MFOPTIM is characteristic of the beam in question and not of the total dose distribution. In the case of opposing beams one would prefer to add to the incident dose the exit dose of the other beam and use this value for the criterion of high dose regions distant from the target area.

An improvement of the planning procedure concerns the location of the isocentre inside the target area. The best location of the isocentre is not always the same for all combinations of incidence directions. A modification of MFSEARCH will be undertaken in which the hand-chosen location of the isocentre will be considered for each combination of incidence directions and if necessary will be changed by the program itself.

The mean cost of a three-field plan, determined by all three programs, is about Dfl 35 (£6), including the use of the terminal. Use of a commercial time-sharing system situated in our department will probably double these costs, but even then they remain acceptable considering the achievement of the planning procedure.

REFERENCES

Allewaert, J. A., 1972. Computation of two-dimensional dose distributions in Co-60 teletherapy with coplanar beams. *Physics in Medicine and Biology*, *17*, 613–623.

Bahr, G. K., Kereiakes, J. G., Horwitz, H., Finney, R., Galvin, J., and Goode, K., 1968. The method of linear programming applied to radiation treatment planning. *Radiology*, *91*, 686–693.

Bentley, R. E., and Milan, J., 1971. An interactive digital computer system for radiotherapy treatment planning. *British Journal of Radiology*, *44*, 826–833.

Gallagher, T. L., 1967. Optimization of external radiation beams for therapy planning. From Ph.D. thesis, Washington Univ., St. Louis, Mo.

Hope, C. S., Laurie, J., Orr, J. S., and Halnan, K. E., 1967. Optimization of X-ray treatment planning by computer judgement. *Physics in Medicine and Biology*, *12*, 531–542.

Hope, C. S., and Orr, J. S., 1965. Computer optimization of 4 MeV treatment planning. *Physics in Medicine and Biology*, *10*, 365–373.

Jameson, D. G., and Trevelyan, A., 1969. A computer approach to dose calculation for supplementary beam therapy. *British Journal of Radiology*, *42*, 57–60.

Mauderli, W., and Fitzgerald, L. T., 1965. A computer program for rotational treatment planning. *American Journal of Roentgenology*, *94*, 880–887.

Stirling, T. D., Perry, H., and Katz, L., 1964. Automation of radiation treatment planning. IV. Derivation of a mathematical expression for the per cent depth dose surface of cobalt 60 beams and visualisation of multiple field distributions. *British Journal of Radiology*, *37*, 544–550.

Van de Geyn, J., 1965. The computation of two- and three-dimensional dose distributions in cobalt 60 teletherapy. *British Journal of Radiology*, *38*, 369–377.

Wood, R. G., 1974. Optimization of treatment plans. In *Computers in Radiotherapy-Physical Aspects* (Butterworth and Co., London).

Book review

Roentgen Appearance of the Hand in Diffuse Disease. By H. L. Steinbach, R. H. Gold and L. Preger, pp. 674, 1975 (Year Book Medical Publishers), £26·30.

Diagnosing systemic disease from X-ray films of the hands has always been a most satisfying experience. Several monographs devoted to the hand have appeared in recent years, but this book is unique in that it also describes in considerable detail the clinical, laboratory, pathological and genetic aspects of the various disorders as well as discussing the skeletal radiology of the remainder of the body. "So much written about so little" is, as the authors themselves observe in their preface, an obvious criticism. Were it not for the cost, no one would quibble at being provided with all this information in one book. But few individuals will wish to spend £26 on such a limited aspect of radiology. However, putting cost aside there is no doubt that there is much to admire in this book. It is well written, with numerous references. Unlike Poznanski's *The Hand in Radiologic Diagnosis*, where the acquired diseases were relatively neglected compared to the superb account of congenital problems, the present volume covers all aspects including the arthritides equally well. The illustrations, which are grouped together at the back of the book, have detailed captions, and can be used as a reference atlas. The main advantage of such a format is the ease with which one can attempt to make a diagnosis when confronted with a problem film. It is, however, extremely annoying to be forced to continually flick backwards and forwards to correlate text with illustration.

If you require a book on congenital disorders, Poznanski's book is better value, but if you wish to have a comprehensive account of all aspects of the radiology of the hand in diffuse disease then this book is an excellent but expensive choice.

P. Armstrong.

1976, *British Journal of Radiology*, *49*, 458–462

Change in oxygen enhancement ratio with depth in tissue-equivalent material for a collimated beam of fast neutrons

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(*Received July, 1975*)

ABSTRACT

Survival of reproductive capacity of murine leukaemia P-388 cells was assayed *in vivo* after the cells had been irradiated *in vitro* under aerobic or hypoxic conditions with collimated beams of X rays or 16 MeV D-Be fast neutrons at various depths in tissue-equivalent phantom material. The response to X-irradiation was the same in the absence of the phantom and at 8·7 cm depth. The response to fast neutrons under aerobic conditions was unchanged from 0 to 23 cm depth within the phantom. However, under hypoxic conditions, the dose-response curve for fast neutrons became significantly steeper with increasing depth in the phantom. The OER decreased from 2·0 in the absence of the phantom to 1·5 at 15 cm deep.

An important question arising from the use of fast neutron beams for radiotherapy is whether there is any significant change in radiation quality as the beam passes into the patient or phantom. Such a change might result from the following processes: differential filtration of the incident beam, increase in the fluence of low-energy neutrons due to scattering, and increase in the proportion of the total dose represented by γ rays. Experimental information on whether the resulting changes in radiation quality are biologically significant is at present conflicting. McNally and Bewley (1969) and Nias *et al.* (1971) could find no evidence of any significant change. On the other hand Berry (1971) found a significant reduction in oxygen enhancement ratio (OER) when cells were irradiated at 10 cm deep in phantom compared to irradiations in the absence of a phantom, while Broerse *et al.* (1971) noted changes in the response of bone-marrow colony-forming units to neutrons of nominal energy 14–15 MeV when a "free-air geometry" was changed to one involving a collimated beam in which 10–20 per cent of the dose was given by scattered neutrons. The present paper presents the results of new experiments made under better conditions than those of Berry (1971) and covering a wider variety of depths in the phantom.

In the previous experiments, cells of the murine leukaemia P-388 were exposed to collimated beams of fast neutrons from a variety of sources as part of a collaborative effort to measure the physical and biological parameters of neutron beams of different energies. This project was co-ordinated by Professor J. T. Brennan of the University of Pennsylvania Hospital, and was designed to answer the question "Is there an optimum fast neutron source for clinical radiotherapy?" (Brennan, 1969). Regrettably, the data obtained in these studies have never been published in full. An unexpected decrease in hypoxic protection against cell-killing by 6–24 MeV neutons was seen when the cells were irradiated at 10 cm deep in a tissue-equivalent phantom, as compared with irradiation with no phantom present (Berry, 1971). These experiments were carried out "in the field" at fast neutron generators far distant from the experimenters' home laboratories (Livermore, California; College Station, Texas; Bethesda, Maryland; Hammersmith Hospital, London) and the assay of survival of cell-reproductive capacity was always *in vivo*. However, because of operational difficulties, irradiation under *aerobic* conditions was delivered to tumour cells held *in vitro*, whilst irradiation under hypoxic conditions was carried out *in vivo* to take advantage of the physiological hypoxia prevailing in the ascitic fluid in seven-day tumour-bearing donor mice (Berry and Andrews, 1961; Berry, 1968). It is conceivable that this difference in geometry may have influenced the values of OER measured in and out of the phantom. We have now made fresh measurements using the same cell system but with all irradiations carried out *in vitro*. Most of the measurements were made using fast neutrons from the M.R.C. cyclotron at Hammersmith Hospital, and additional experiments were done with X rays generated at 8 MV. The irradiation set-up was the same as that of McNally and Bewley (1969).

MATERIALS AND METHODS

The P-388 lymphocytic leukaemia of the DBA/2 mouse, techniques for maintaining cells *in vitro* and the assessment of cell reproductive capacity by serial dilution-assay *in vivo* in isologous recipient mice have been described previously (Berry and Andrews, 1961; Berry 1968). For the present experiments, the tumour cells were suspended in a complete holding medium composed of Fischers Medium (Gibco) supplemented with 15 per cent fetal calf serum (Flow), at a concentration *circa*

5×10^6 cells/ml., immediately before placing them in Perspex tubes of 0·8 cm internal diameter and 0·2 cm wall thickness, through which air or white-spot purity nitrogen (plus 5 per cent carbon dioxide) was bubbled. Silicone anti-foam was added to the suspension at a final concentration of 1:6,000. The cell suspensions were allowed to equilibrate with the gas mixture for a minimum period of 15–20 minutes, at which time a small aliquot was removed as the unirradiated control and the irradiation started.

The tubes were exposed in pairs, side by side, samples being removed at suitable intervals as the doses were accumulated. The dose-rates while the beam was on were about 37 rad/minute with X rays and 25 rad/minute with neutrons, and the beam current was adjusted so that the dose-rates were similar for experiments in and out of the phantom. The duration of exposures for the highest doses in aerobic and hypoxic conditions were respectively about 40 minutes and one and a half hours, except at 23 cm deep in the phantom where it was impossible to complete the neutron irradiation in one and a half hours; in this position the cells were only irradiated aerobically and the total duration of exposure for the highest dose was three hours ten minutes.

The source of neutrons was the M.R.C. cyclotron, which gives a beam of mean energy 7·5 MeV (Parnell, 1972). The front of the phantom was placed at the standard treatment distance, namely 120 cm from the target. The field size was usually 16×16 cm but sometimes 10×10 cm. The pair of tubes was placed at various depths in the phantom, and at 120 cm with no phantom present.

The source of X rays was the M.R.C. 8 MeV linear accelerator, and for these exposures the phantom was placed 100 cm from the target with a field size of 20×20 cm. For exposures with no phantom present, a sheet of Perspex 1·3 cm thick was placed in front of the tubes to give secondary-electron equilibrium.

Immediately after irradiation, the tumour cells were diluted with additional complete holding medium to a concentration of $5\text{–}10\times10^5$ cells/ml. and maintained at room temperature during the return journey to Oxford for counting, appropriate dilution in Hanks BSS and intraperitoneal injection into isologous recipient mice (total elapsed time two to four hours). All animals which died within the subsequent 100-day period with ascites were considered positive; those which died without gross ascitic tumour were submitted to autopsy, and unless the presence of a solid tumour due to accidental intramuscular injection was confirmed they were excluded from the data. The 100 day assay period was chosen as it significantly exceeds the maximum time for one irradiated tumour cell to proliferate to cause death of the recipient animal, even in the presence of heritable sub-lethal radiation damage (Berry, 1967; 1972).

The doses quoted in the results represent the doses of neutrons at the cells, *i.e.* corrected for attenuation in the phantom. The additional dose of γ rays is not included but is shown in Table I, as a per cent of the neutron dose at the position of the cells. The dosimetric methods used were described by Bewley and Parnell (1969). Percentage depth doses of neutrons were taken from isodose charts

TABLE I

SUMMARY OF SURVIVAL-CURVE PARAMETERS WITH SEPARATE AIR AND NITROGEN CONTROLS

	Field size cm	D_γ/D_n (per cent)	Extrapolation number	Aerobic *Do* (rads)	Anaerobic *Do* (rads)	OER
X rays						
No phantom	20×20	—	2·9 (1·4–6·1)	140 (123–162)	363 (313–433)	2·59 (2·28–2·96)
8·7 cm deep	20×20	—	2·9 (1·4–6·1)	140 (123–162)	370 (318–443)	2·64 (2·33–3·03)
Neutrons						
No phantom	10×10	4	2·0 (1·2–3·4)	75 (69–81)	150 (132–174)	2·01 (1·80–2·27)
Depth 0	10×10	5	2·0 (1·2–3·4)	75 (69–81)	178 (148–222)	2·38 (2·02–2·91)
1·5	16×16	7	2·0 (1·2–3·4)	75 (69–81)	129 (114–149)	1·73 (1·54–1·97)
8·7	12×12 10×10	10	2·0 (1·2–3·4)	75 (69–81)	125 (109–145)	1·67 (1·48–1·91)
15·5	16×16	17	2·0 (1·2–3·4)	75 (69–81)	111 (100–126)	1·49 (1·34–1·67)
23·3	16×16	24	2·0 (1·2–3·4)	75 (69–81)	—	—

Figures in brackets represent 95 per cent confidence limits.

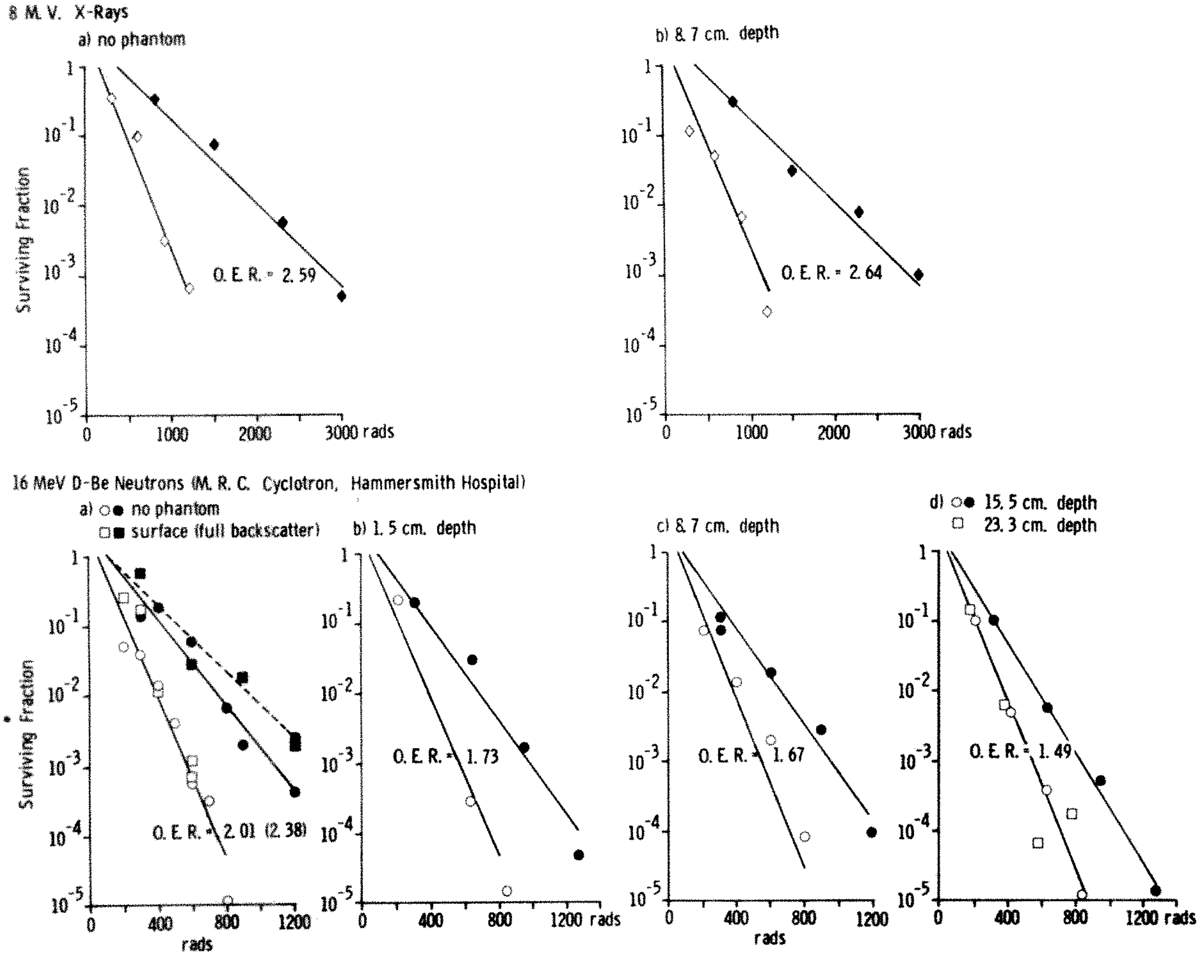

FIG. 1.

Survival of reproductive capacity of murine P-388 leukaemia cells irradiated with X rays generated at 8 MV or fast neutrons generated with 16 MeV deuterons on Be, at various depths in a tissue-equivalent phantom. Each point represents an individual serial dilution-assay using 15–39 isologous recipient mice. Survival curves are fitted to the data by the method of Pike and Alper (1964); the parameters of these curves are summarized in Table I.

measured with a compensated ionization chamber in a phantom filled with tissue-equivalent liquid. The partial dose of γ radiation was measured with a Geiger-Müller counter shielded with ^{6}Li metal to exclude thermal neutrons.

RESULTS

The proportion of morphologically typical tumour cells which were in fact reproductively intact was determined by the method of Porter and Berry (1963) both for irradiated cells and for unirradiated P-388 leukaemia cells which had been held *in vitro* and treated exactly as were the irradiated cells. The survival of these controls held in nitrogen was a little lower than that of controls held in air. From eight assays involving 150 recipient animals the proportion of tumour cells reproductively intact (equivalent to plating efficiency) was 6 per cent in nitrogen and 11 per cent in air. These values are not significantly different but we thought it best to use the separate control values rather than the pooled results.

Survival curves have been fitted to the data by the method of Pike and Alper (1964); these are shown in Fig. 1, and their parameters are summarized in Table I. Use of pooled controls would reduce all values of OER by about 0·2. For irradiation with 8 MV X rays there was no significant change in survival-curve parameters for irradiation in the absence of the phantom or at a depth of 8·7 cm in the

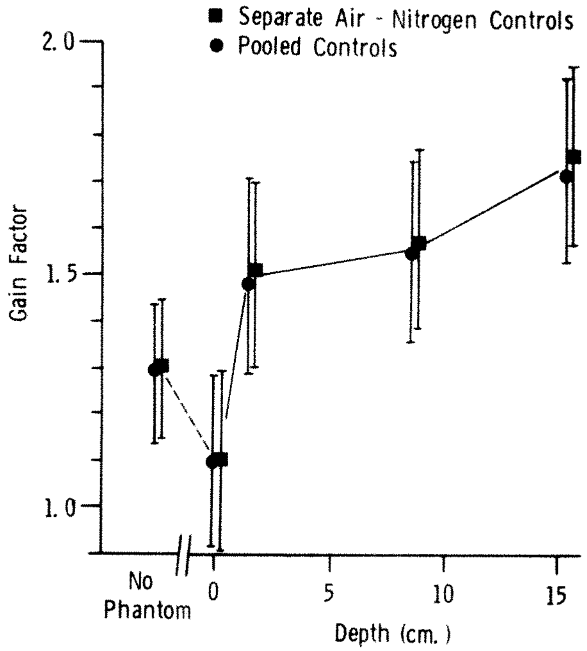

FIG. 2.
Anoxic Gain Factor as a function of depth in the phantom. The gain factor is the ratio OER for X rays divided by OER for neutrons.

tissue-equivalent liquid, and the values of the OER are comparable with previous measurements using the same P-388 leukaemia cells (Berry and Andrews, 1961; Berry, 1968). For irradiation with fast neutrons from the M.R.C. cyclotron, the slope of the survival curve for cells irradiated under aerobic conditions was unchanged at all depths in the tissue-equivalent phantom (so that it was statistically acceptable to fit a common curve to the data at all depths from 0–23·3 cm). However, the slope of the survival curve for cells irradiated in nitrogen became steeper with increasing depth in the phantom and the OER was correspondingly progressively reduced (Table I). The results with full backscatter at the surface of the phantom are not significantly different from those in the absence of the phantom. In Fig. 2 the Anoxic Gain Factor (m_x/m_n where m is the OER) is plotted as a function of depth in the phantom. Use of separate controls increases all values of OER in the same way and leaves the Anoxic Gain Factor unchanged.

DISCUSSION

The present results confirm the earlier observation that the response of P-388 leukaemia cells to irradiation with fast neutrons of 7–25 MeV mean energy is less affected by the presence or absence of oxygen when the cells are irradiated at a depth in a tissue-equivalent phantom than when they are irradiated in the absence of the phantom (Berry, 1971). The regularity of the change in anoxic sensitivity with depth and the lack of any similar change when irradiated with X rays makes it difficult to suppose that the results could be due to some unsuspected factor having a differential effect in and out of the phantom. This change in the biological effect of collimated beams of fast neutrons takes place in the absence of any obvious change in neutron spectrum above 2 MeV (Field and Parnell, 1965) and in spite of an increase in the γ-ray contribution to the total dose which would of itself increase the OER. Such a change in hypoxic protection at a depth in tissue would increase significantly the potential therapeutic gain factor in the treatment by fast neutrons of deep-seated tumours containing significant numbers of hypoxic cells. However, at least two other cell lines of tumour origin show no change in OER, or indeed in any of the parameters of the response, when irradiated at different depths in tissue-equivalent material exposed to a collimated beam of fast neutrons (McNally and Bewley; 1969, Nias *et al.*, 1971). By contrast, two experiments have shown an increase in RBE under aerobic conditions when the neutron spectrum was modified by the addition of a lower energy component. Railton *et al.* (1973) modified a beam of 14 MeV neutrons with a ^{235}U converter plate and found an increase in the RBE of Chinese hamster ovary cells irradiated *in vitro* but no change in OER. Broerse *et al.* (1971) noted a significant increase in the radiosensitivity of mouse bone-marrow colony-forming units *in vivo* as a result of collimating a beam of 14 MeV neutrons. The addition of the collimator produced only a small change in the neutron spectrum compared to the change introduced by Railton *et al.* (1973) with the converter plate. In addition, recent experiments with Ehrlich ascites cells, using the same set-up as was used in the experiments described in the present paper, suggested a small *increase* in OER when the cells were irradiated with fast neutrons at a depth of 8·7 cm in a phantom (Bewley *et al.*, 1975).

This variation of observed response prevents any simple statement of "rules" for mammalian cells. The change in response of P-388 cells to fast neutrons at a depth in tissue may reflect quite subtle changes in neutron spectrum. It may be of relevance that the only cell types which appear to be exquisitely sensitive to changes in neutron spectrum, the P-388 leukaemia cells and the bone-marrow colony-forming units, were both derived initially from haemopoietic tissue. Clearly a wider variety of cells both from tumours and normal tissue needs to be irradiated with fast neutrons of different energies and in collimated beams of fast neutrons at various depths in tissue-equivalent materials. However, the variation in response of murine P-388 leukaemia cells to irradiation with charged particle track segments of varying and known ionization density correlates with the difference between the response of these cells and that of human kidney-derived T-1 cells to fast neutrons of different energies (Berry, 1970).

For P-388 cells, the OER decreases to *circa* 1·0 at LET values around 90 keV/μm and the OER for exposure to fission-spectrum fast neutrons (for which the majority of ionizing events are *circa* 50–100 keV/μm) is close to 1. By contrast, for T-1 cells the OER remains in excess of 1·5 to ionization densities above 100 keV/μm and this is reflected in an OER around 1·5 for exposure to fission-spectrum neutrons (Berry, 1970; 1971).

REFERENCES

Berry, R. J., 1967. "Small clones" in irradiated tumour cells *in vivo*. Kinetics of regrowth of murine leukaemia cells surviving irradiation with X rays, fast neutrons and accelerated charged particles. *British Journal of Radiology*, *40*, 285–291.

1968. Hypoxic protection and recovery in tumour cells irradiated at low dose-rates and assessed *in vivo*. *British Journal of Radiology*, *41*, 921–926.

1970. Survival of murine leukaemia cells *in vivo* after irradiation *in vitro* under aerobic and hypoxic conditions with mono-energetic accelerated charged particles. *Radiation Research*, *44*, 237–247.

1971. Hypoxic protection against fast neutrons of different energies—a review. *European Journal of Cancer*, *7*, 145–152.

1972. Differences in LET dependence of cell killing and the production of heritable non-lethal damage in mammalian systems. In *Radiobiological Applications of Neutron Irradiation*, pp. 89–98 (I.A.E.A. S.T.I./PUB/325, Vienna).

Berry, R. J., and Andrews, J. R., 1961. Quantitative relationships between radiation dose and the reproductive capacity of tumor cells in a mammalian system *in vivo*. *Radiology*, *77*, 824–830.

Bewley, D. K., and Parnell, C. J., 1969. The fast neutron beam from the M.R.C. Cyclotron. *British Journal of Radiology*, *42*, 281–288.

Bewley, D. K., Cullen, B., Field, S. B., Hornsey, S., and Page, B. C., and Berry, R. J., 1976. A comparison for use in radiotherapy of neutron beams generated with 16 and 42 MeV deutrons on beryllium. *British Journal of Radiology*, *49*, 360–366.

Brennan, J. T., 1969. Fast neutrons for radiation therapy. *Radiologic Clinics of North America*, *7*, 365–374.

Broerse, J. J., Engels, A. C., Lelieveld, P., van Putten, L. M., Duncan, W., Greene, D., Massey, J. B., Gilbert, C. W., Hendry, J. H., and Howard, A., 1971. The survival of colony-forming units in mouse bone marrow after *in vivo* irradiation with D-T neutrons, X- and gamma radiation. *International Journal of Radiation Biology*, *19*, 101–110.

Field, S. B., and Parnell, C. J., 1965. The use of threshold detectors to determine changes in a fast neutron energy spectrum with depth in a phantom. *British Journal of Radiology*, *38*, 618–621.

McNally, N. J., and Bewley, D. K., 1969. A biological dosimeter using mammalian cells in tissue culture and its use in obtaining neutron depth dose curves. *British Journal of Radiology*, *42*, 289–294.

Nias, A. H. W., Greene D., and Major, D., 1971. Constancy of biological parameters in a 14 MeV neutron field. *International Journal of Radiation Biology*, *20*, 145–151.

Parnell, C. J., 1972. A fast neutron spectrometer and its use in determining the energy spectra of some cyclotron-produced fast neutron beams. *British Journal of Radiology*, *45*, 452–460.

Pike, M. C., and Alper, T., 1964. A method for determining dose-modification factors. *British Journal of Radiology*, *37*, 458–462.

Porter, E. H., and Berry, R. J., 1963. The efficient design of transplantable tumour assays. *British Journal of Cancer*, *17*, 583–595.

Railton, R., Lawson, R. C., Porter, D., and Hannan, W. J., 1973. Neutron spectrum dependence of r.b.e. and o.e.r. values. *International Journal of Radiation Biology*, *23*, 509–518.

1976, *British Journal of Radiology*, *49*, 463–464 MAY 1976

Technical notes

Technique for demonstration of Polaroid photographs

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The increasing use of Polaroid photographs to record images obtained by various imaging techniques, such as isotope and ultrasound scanning and computer-assisted tomography, poses difficulties of display for teaching purposes. The passing from hand to hand of a number of small photographs precludes the demonstration and discussion of the images in a detailed way. The problem of loss of valuable clinical records or teaching material is an additional consideration. While the use of projection slides or an overhead projector is suitable for large groups, meeting in a suitably equipped room, they are inappropriate for the less formal tutorial situation, or for demonstration on ward rounds. To overcome these problems, a method of transfer of the photographic images on to X-ray film has been devised. The method is simple, flexible, and has been found suitable and convenient for demonstration of scans to small groups.

The method consists in photographing the Polaroid prints onto 35 mm negative film, developing the film in the normal way, and projecting the negative image by means of a photographic enlarger onto X-ray film, which is then processed in an automatic processor. The camera is mounted on a vertical column and can be moved nearer to, or further from, the Polaroid print which is held flat on a baseboard by a thin sheet of glass. The print is illuminated from the side by two lamps, set at 45 deg. to the baseboard (Fig. 1).

The film used is a 125ASA panchromatic film such as Ilford FP4. It is developed in a moderately fine-grain developer such as Kodak D76, Ilford ID11 or Microphen, or Paterson's Acutol.

The negative image is then projected by an enlarger onto X-ray film (Fig. 2). Various types of film, including single-emulsion and copy film have been tried. The blue base of Kodak Blue Brand R.P. 54 film gives a tone range which of those films tried approximates most closely to that of Polaroid prints.

The use of X-ray film has a number of advantages:

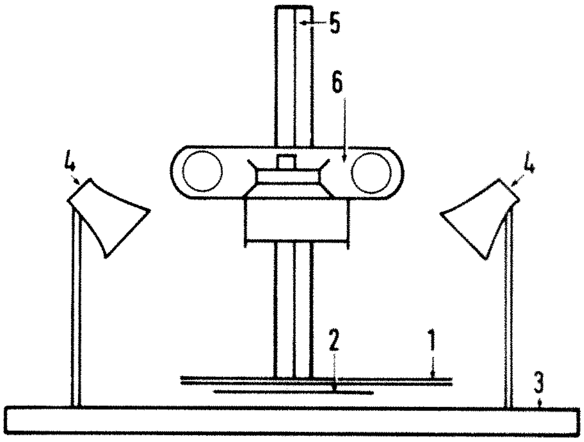
(1) It is readily available in X-ray departments in a wide range of sizes.
(2) It is easy to process in an X-ray department.
(3) Its base is sufficiently rigid to allow ready demonstration on standard viewing boxes.
(4) The emulsion is durable and resists damage.

Disadvantages are:

1. The high sensitivity of the emulsion to light which makes the use of a neutral grey filter in the enlarger necessary to achieve controllable exposures (*e.g.* five to ten seconds at *f*5.6).

A suitable filter may be made from a piece of non-screen X-ray film given a "fogging" exposure. The filter the author uses was made by so exposing a sheet of 3M Type S non-screen film, with a single envelope packaging, at a tube-film distance of 100 cm at 70 kV 60 mAs. A piece of black card is placed on the enlarger baseboard to prolong exposure time by reducing reflected light.

2. The theoretical unsharpness due to projection of the image onto film with emulsion on both sides separated by a finite distance, resulting in two images of slightly different size superimposed on each other, has proved to be a theoretical rather than a



1. THIN SHEET of GLASS.
2. POLAROID PRINT.
3. BASEBOARD.
4. LAMP SET at 45° to BASEBOARD.
5. VERTICAL COLUMN for MOUNTING CAMERA.
6. CAMERA MOUNTED on VERTICAL COLUMN.

FIG. 1.

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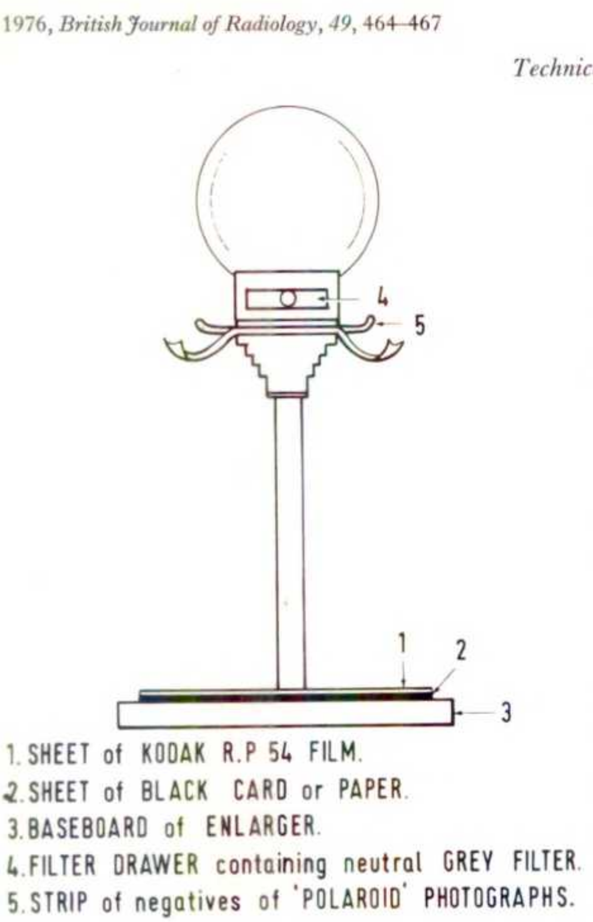
4
5
1
2
3
1. SHEET of KODAK R.P 54 FILM.
2. SHEET of BLACK CARD or PAPER.
3. BASEBOARD of ENLARGER.
4. FILTER DRAWER containing neutral GREY FILTER.
5. STRIP of negatives of 'POLAROID' PHOTOGRAPHS.

FIG. 2.

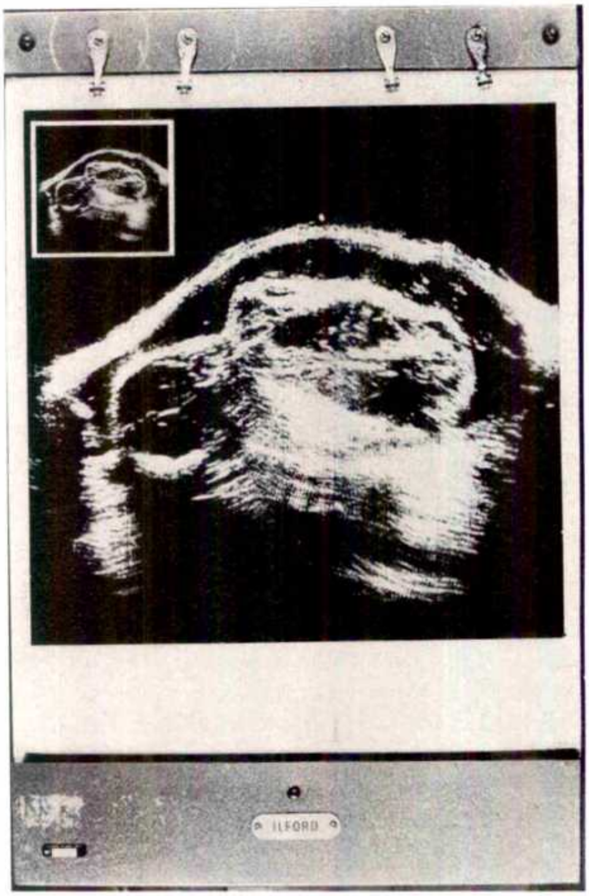

FIG. 3.

Enlargement of ultrasound scan of a pregnancy onto 14 in. square film. The inset shows the relative size of the original Polaroid photograph. The film view-box is included for relative scale.

practical problem, no lack of sharpness being noticeable.

The image produced in the emulsion on the underside of the film lying on the black card on the enlarger baseboard, mentioned above, is presumably fainter than that on the uppermost side, and this probably reduces the possibility of noticeable unsharpness due to two images.

The author uses a Pentax SP500 single-lens-reflex camera, with a built-in through-the-lens exposure-meter, and a Zenith UPA5 portable enlarger. The latter can easily be set up in an X-ray darkroom, thereby enabling the easy and immediate checking of results, as film-processing facilities are to hand and any alterations in exposure deemed necessary can be made.

ACKNOWLEDGMENTS

I wish to thank Mr. E. Turnbull, S.R.N., for preparation of Figs. 1 and 2, and Mr. J. Hancock for preparation of Fig. 3.

A Monte Carlo approach to the accuracy of cell-survival curves

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(*Received October, 1975 and in revised form January, 1976*)

The application of statistics to biological problems can present considerable difficulties to the biologist particularly when the problem does not conform exactly to a standard textbook method. These difficulties can, to some extent, be circumvented using random numbers (Monte Carlo method) to provide a direct approach that does not involve a detailed mathematical knowledge of statistics and which provides useful quantitative information about the errors arising under specific conditions.

The method involves constructing a computer program that will generate artificial survival curves for any type of desired survival equation assuming particular values for the equation parameters; for instance, a simple multitarget equation with chosen values of D_0 and N. The exact survival values are calculated for specified radiation doses and then "experimental error" is introduced by altering the values calculated, in a random manner, in such a way that they conform to a particular probability distribution with a specified standard deviation. By generating many of these curves and obtaining estimates of the value of D_0 and N for each curve, using whichever curve-fitting method that is required, one can obtain a frequency distribution of the estimated values of D_0 and N. By this means one can quite straightforwardly investigate the importance of a wide variety of factors which influence the accuracy of the estimates of radiobiological parameters.

For instance, the method allows one to combine errors that conform to different probability distributions such as the Poisson distribution for the random nature of cell colony counts and a log-normal distribution for survival as a result of a normal distribution in radiation dose. Linear regression requires theoretically that the survival values are independent measurements and so each should be based on a separate set of control data. In practice, only one set is used for all the survival values in one experiment, and the extent to which this influences the estimates of D_0 and N and their standard errors can be examined.

One can investigate the effect of employing different criteria for the best fit to the survival points, such as χ^2 or even the statistically inadmissible use of the simple sum of the deviations from the mean, which has the effect of giving much less statistical weight to the "way out" survival values that are the bugbear of the experimenter.

The effect of different mathematical transformations of the survival when using linear regression can also be compared. For instance, for the simple multitarget equation the $\ln(-\ln(1-S))$ transformation considered by Gilbert (1974) is linear down to lower radiation doses than the conventional $\ln S$ transformation provided that N is large, while $\ln S$ is linear for all doses if $N=1$. It is readily ascertained which is the better of these two transformations under specific conditions and how much bias in the estimates is likely to occur.

The simple Monte Carlo method described can also be of use for investigating the validity of more complicated statistical procedures. A particular example is the Pike-Alper program (1964), which is used for determining "dose modifying factors" (ratio of D_0 values when two survival curves are assumed to have the same extrapolation number). This program first calculates D_0 and N for the two survival curves by linear regression on the linear part of the survival curve. It then fits the same data, assuming that the two curves have a common value of N, and using the F-test for comparing variances determines whether this second fit, with only three parameters, is statistically worse than the first, four-parameter, fit at the 5 per cent level of probability. If the three-parameter fit is not significantly worse than the four-parameter fit (it can never be better), the D_0 ratio, assuming a common N, is taken as the best estimate of the dose modifying factor.

Consider, first of all, two survival curves with the same $N=2$ and different D_0 values of 100 and 300 rad. Assuming the first curve had five points over the range 300–700 rad and the second curve five points over the range 900–2,100 rad and that survival was log normally distributed with a standard deviation equal to 20 per cent of the mean survival, 200 pairs of curves were generated and fitted as outlined above. Of these 200 "experimental" curves, nine were rejected as having different N values and the ratio of the D_0 values for the remainder was 3·00 with a standard deviation of 0·09 when a common N was assumed. The ratio of the D_0 values for direct linear regression was 2·99 with a standard deviation of 0·32, which bears out the statement by Pike and Alper (1964) that when the true N values are the same the method gives a more precise estimate of the dose modifying factor.

Now consider the case where the N values were not equal, by making a single change to the previous example. By assuming that the $D_0=300$ rad curve had $N=1$ instead of 2 we obtained the distribution shown in Fig. 1. Of the 200 pairs of curves, 150 were accepted as having a common N and the two distributions were moved towards each other compared to the distributions when direct linear regression was used. This is because on average the greater N value belongs to the $D_0=100$ curve, and assumption of a common N will increase the D_0 estimate, while the opposite occurs with the $D_0=300$ curve; thus the ratio of the D_0 values tends to be reduced (Fig. 1d). The ratio of the D_0 values, assuming a common N, is shifted so that the mean is at 2·64 compared to the true value of 3·00, and not one of the 150 individual ratios is as great as the true value.

This second case demonstrates that, under circumstances which might well occur in practice, use of the Pike-Alper program can lead to an appreciable systematic error (well beyond the expected standard error) in estimating the D_0 ratio of two survival curves, if in fact the N values are not equal.

Indeed worse data can lead to an apparently more accurate D_0 ratio. For instance, if an experiment is repeated it may be found that one experiment does not permit a common N to be assumed, whereas the other experiment, with a slightly larger variation, does allow a common N to be assumed. The Pike-Alper program will then usually give a smaller standard deviation for the less accurate results.

It is not fully apparent to us why the statistical test employed for justifying the assumption of a common N is inadequate. It can be argued that failure to show that a difference between the estimates of two values of N is statistically significant at the 5 per cent level of significance is not sufficient for one to conclude that they are equal. Surprisingly, however, making the test for a common N more stringent, by increasing the level of probability above which pairs of curves are accepted as having a common N, does not improve the estimate of the D_0 ratio (Table I). It is evident, therefore, that use of the Pike-Alper program is justified only when there is external evidence that the two survival curves have the same value of N, and then it will give a useful increase in accuracy.

TABLE I

RATIO OF D_0 VALUES FOR DIFFERENT LEVELS OF PROBABILITY USED IN ACCEPTING CURVES WITH A COMMON N AND ALSO THE RATIO WHEN A COMMON N IS NOT ASSUMED.

Probability $\geqslant$	D_0'/D_0	Standard deviation	No. of pairs of curves accepted
0	2·64	0·07	200
0·05	2·64	0·07	150
0·1	2·64	0·08	128
0·3	2·65	0·08	62
Without assuming a common N	3·03	0·29	200

The examples outlined illustrate the usefulness of a simple computer program using random numbers for estimating the accuracy of estimates of cell-survival curve parameters and the ease with which quite complex and intractable problems can be analysed directly to give quantitative answers to specific questions, with only a rudimentary knowledge of the mathematics of statistics. Furthermore, the need to specify the magnitude and distribution of errors that may influence experimental results has a salutary effect in forcing the experimenter to consider the various sources of error to which his results are subject.

REFERENCES

GILBERT, C. S., 1974. A double minus log transformation of mortality probabilities. *International Journal of Radiation Biology 25*, 633–634.

PIKE, M. C., and ALPER, T., 1964. A method for determining dose-modification factors. *British Journal of Radiology, 37*, 458–462.

1976, *British Journal of Radiology*, *49*, 468

Case report

A vascular ureterogram

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(*Received October 1975*)

CASE HISTORY

An eight-year-old boy had always done less well than his healthy twin brother. He was found to be in renal failure, with a blood urea of 18 mmol./l., and glomerular filtration rate of 9 ml./minute (corrected EDTA clearance). The clinical diagnosis was an incomplete variant of the prune-belly syndrome. On the early films of the renal areas the intravenous urogram showed haloes of contrast medium outlining radiolucent spaces, and these spaces were opacified by 24 hours (Fig. 1). They were misinterpreted as distended calices. Their linear shape and infero-medial position should be noted, not in keeping with this diagnosis.

On surgical exploration the ureters were dilated, tortuous, and rather inflamed. Both kidneys were small, lying well above the contrast shadows seen. In retrospect the early films therefore showed the opacified walls of the abnormal ureters. This effect has been called whole-body opacification and derives from contrast medium in the intravascular and also interstitial (extracellular) space. It can be very useful for outlining avascular cystic spaces in the infant. In our patient the grossly dilated ureters of the prune belly syndrome were lit up in this way, and confused with the well-known "shell nephrogram" of distended non-opacified calices.

REFERENCE

MARTIN, D. J., GRISCOM, N. T., and NEUHAUSER, E. B. D., 1972. A further look at the total body opacification effect. *British Journal of Radiology*, *45*, 185–192.

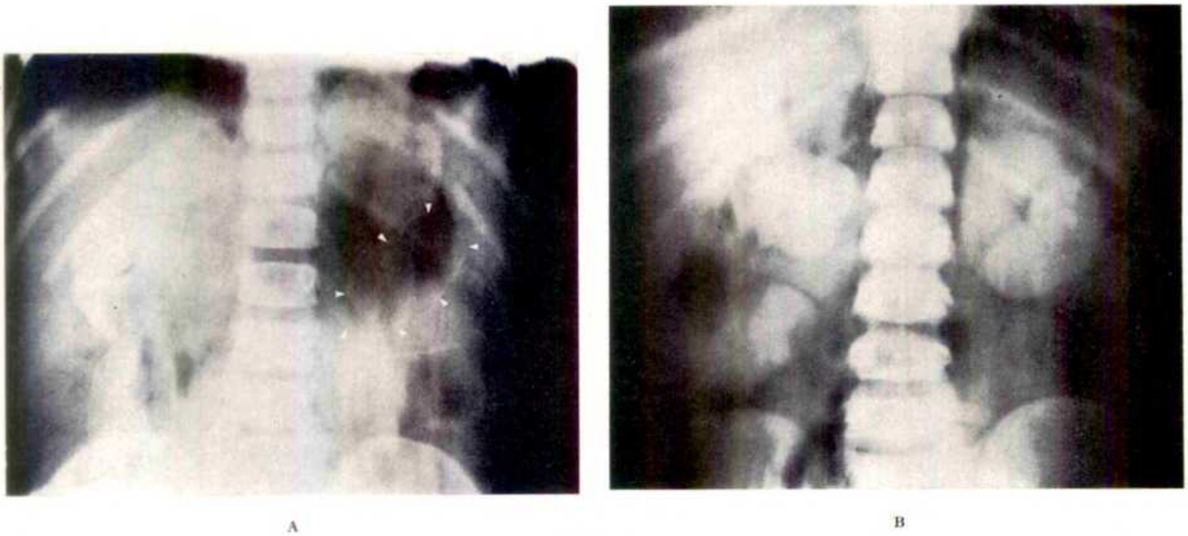

FIG. 1.

(A) Intravenous urogram—ten-minute film. Contrast medium outlines the walls of the tortuous, dilated ureters (arrows). The kidneys are above, small, and poorly opacified.

(B) The 24-hour film shows the ureters opacified—these are *not* distended calices.

1976, *British Journal of Radiology*, *49*, 469–474 MAY 1976

Proceedings of The British Institute of Radiology

Radio-isotopic and radiological investigation of regional lung function*

Abstracts of papers read at a meeting held at the Edward Lewis Theatre, Middlesex Hospital Medical School, London, W.1, on Wednesday, October 15, 1975.

Physiological aspects of regional pulmonary blood flow, by J. M. B. Hughes.
Radiological assessment of regional blood flow, by D. H. Trapnell.
Clinical applications and limitations of lung perfusion scans, by D. N. Croft.
Gamma-ray densitometry, by V. G. Cattrell.
Changes in blood flow and ventilation parameters in the lung of the pig after local X-irradiation, by H. F. Moustafa and J. W. Hopewell.
Evaluation of a new macroaggregated albumin kit for lung scanning and its comparison with other agents by W. J. Hannan, J. D. Simpson, P. Tothill and M. V. Merrick.
The distribution of pulmonary oedema, by I. H. Kerr.
Measurements of regional lung water with $H_2\,^{15}O$, by F. Fazio, C. G. MacArthur, C. G. Rhodes, T. Jones and J. M. B.Hughes.
Measurement of lung water in shock lung and other clinical states, by W. A. Crosbie.
The relative contribution of thoracic cage and diaphragm movement to regional lung function, by J. B. Ridyard and R. Stewart.
Analysis of ventilation distribution using a gamma camera, by D. Ackery.
The use of the short-lived radioactive gas $^{81}Kr^m$ for studying regional ventilation: Theoretical aspects, by T. Jones.
The use of short-lived radioactive gas $^{81}Kr^m$ studying regional ventilation: Clinical applications, by J. P. Lavender and F. Fazio.
Ventilation studies in infants, by S. Godfrey.
Physiological determinants of ventilation distribution, by J. M. B. Hughes.
Regional ventilation in asbestos workers, by N. N. Stanley.
Evaluation of regional lung function using the Ohio-Nuclear Regional pulmonary function analyser, by Patricia M. Warren, D. J. Warren, R. J. Hare and A. L. Muir.
An integrated ^{133}Xe regional pulmonary function analyser, by R. G. Rawbone.

PHYSIOLOGICAL ASPECTS OF REGIONAL PULMONARY BLOOD FLOW

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In the last 15 years measurements of regional pulmonary perfusion with radioactive gases or technetium-labelled particles have considerably increased our understanding of some of the factors determining regional pulmonary vascular resistance. Interpretation of patterns of blood flow in normal subjects must take into account some of the special features of the pulmonary circulation such as (a) low pulmonary arterial and venous pressures relative to the height of the lung; (b) low vascular resistance; (c) the "waterfall" effect in the pulmonary capillaries; (d) opposite effects of inflation and deflation of the lung on the dimensions of the capillaries (or alveolar vessels) and the arteries and veins (extra-alveolar vessels). Additionally, in disease local pulmonary blood flow may be affected by (a) vascular obstruction; (b) destruction or narrowing of the vessels; (c) variations in local alveolar oxygen tension. Local vascular resistance may be reduced physiologically by the opening up of new channels (recruitment) and by distension of those already open.

In chronic mitral valve disease the upper zones receive more blood flow per unit volume than the lower zones in the upright position. This reversal of the normal distribution is probably caused, in the chronic situation, by intimal and medial thickening of the arterial vessels in the lower zones which are exposed to the highest vascular pressures. Neither acetylcholine infusion nor changes of lung volume influence this distribution significantly; it is fixed. The factor initiating this reversal of blood flow may be acute pulmonary oedema. In experimental animals alveolar and (to a lesser extent) interstitial oedema in the dependent lung zones is accompanied by a local reduction of blood flow, and in erect man a rapid infusion of dextran causes a redistribution of flow from base to apex. The mechanisms causing these changes are principally vascular narrowing from the increase in fluid pressure in the interstitium but local hypoventilation and hypoxic vasoconstriction may also occur. The mechanisms underlying the redistribution of local blood flow in chronic bronchitis, asthma and bronchial carcinoma have not received much study as yet.

RADIOLOGICAL ASSESSMENT OF REGIONAL BLOOD FLOW

By D. H. Trapnell

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Roehampton and Westminster Hospital

A radiologist assessing blood flow looks at the radiographic shadows of actual pulmonary arteries and veins and, in good quality radiographs, can detect vessels to within about 1–1½ cm of the pleura—that is, to vessels as small or almost as small as the lobular arteries and veins.

The vessels are normally visible because there is air on each side of them. They are consequently best shown by a high kilovoltage technique and are invisible if any disease process displaces the air adjacent to them. In health the proportion of the total shadow contributed by the connective tissue and vessel walls is so small that the approximation of calling the whole shadow a "blood vessel" is justified. In some disease states, such as interstitial oedema, however, a significant proportion of the shadow is produced by perivascular oedema. Fortunately, however, in diseases which produce this "cuffing" of the blood vessels the edges of the vascular shadows are blurred. Thus valid inferences about the calibre of sharply defined vessels may confidently be made.

Reductions of calibre or absence of vessels indicate reduced (or absent) flow in the area. Dilatation of the vessels may or may not mean there is increased flow. Localized dilatation is a valuable sign of localized increase in flow, but if all the vessels appear dilated, the rate of flow may be increased (as in left to right shunt) or it may be decreased (as in polycythaemia rubra vera). Generalized dilatation of vessels may also indicate that the blood volume is increased (as in polycythaemia rubra vera).

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*Reprints available from the Editorial Office

CLINICAL APPLICATIONS AND LIMITATIONS OF LUNG PERFUSION SCANS

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Perfusion lung scans are used mainly for the diagnosis of pulmonary embolism. In this condition, the accuracy of blind reporting and the assessment of the extent of the pulmonary lesion is excellent, and is equal to that of pulmonary angiograms. Tow and Simon (1975) found that none of 296 scans from patients with angiograms demonstrating emboli was normal. Thus, the "false negative" rate is nil and a normal lung perfusion scan is very strong evidence against a pulmonary embolus. Conversely, many pulmonary conditions other than emboli cause perfusion defects. The chest radiograph resolves most of these for it will reveal pneumonia, effusions, carcinoma, etc. In chronic obstructive lung disease (COLD) impaired perfusion occurs secondary to impaired ventilation and in the presence of a normal chest radiograph. In a personal series of 291 patients, COLD was present in 14 per cent (Bateman *et al.*, 1975). In such patients combined ventilation perfusion lung scans are essential (Williams *et al.*, 1974). Ventilation perfusion mismatch correlates well with the clinical diagnosis of pulmonary embolus (78 per cent) (Williams *et al.*, 1974), with the presence of venous thrombosis in the leg (85 per cent) (Browse *et al.*, 1974), and with the pulmonary angiogram evidence of emboli (95 per cent) (McNeil *et al.*, 1974). Perfusion lung scans are helpful in diagnosing pulmonary emboli in most patients, but not in those with COLD in whom a combined ventilation perfusion scan is needed.

REFERENCES

BATEMAN, N. L., GAUNT, J. I., and CROFT D. N., 1975. In preparation. Presented at British Nuclear Medicine Society Annual Meeting, March 20, 1975.

BROWSE, N. L., CLEMENSON, G., and CROFT, D. N., 1974. Fibrinogen-detectable thrombosis in the legs and pulmonary emboli. *British Medical Journal*, *1*, 603–604.

MCNEIL, B. J., HOLMAN, L., and ADELSTEIN, S. J., 1974. The scintigraphic definition of pulmonary embolism. *Journal of the American Medical Association*, *227*, 753–756.

TOW, D. E., and SIMON, A. L., 1975, Comparison of lung scanning and pulmonary angiography in the detection and follow-up of pulmonary embolism: the Urokinase-pulmonary embolism trial experience. *Progress in Cardiovascular Diseases*, *17*, 239–245.

WILLIAMS, O. LYALL, J., VERNON, M., and CROFT, D. N., 1974. Ventilation-perfusion lung scanning for pulmonary emboli. *British Medical Journal*, *1*, 600–602.

GAMMA-RAY DENSITOMETRY

By V. G. Cattrell

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A portable equipment using a source of ^{137}Cs produces a sharply collimated beam of γ rays directed onto a crystal detector. This beam defines a quasi-cylindrical volume in space and an analogue signal is obtained which is proportional to the change in mass per unit area perpendicular to the beam. In a normal chest at tidal breathing the signal has two components:

(1) The "lung pulse" of amplitude 0·1 gm/cm^2 is correlated with heart beat and attributed to distension of blood vessels within the beam as they accommodate part of the stroke volume in systole. With signal averaging a "lung pulse" as low as 0·02 gm/cm^2 is detectable in a patient some 25 gm/cm^2 thick.

(2) The "respiratory signal" of amplitude 0·5 gm/cm^2 is produced by air entering the volume and displacing soft tissue from within the beam. The "lung pulse" and "respiratory signal" can be analysed to reveal changes in mechanical properties of tissue and vessels within the beam.

Dog experiments show that the "lung pulse" disappears with pulmonary artery occlusion, and that in the normal physiological range "lung pulse" amplitude is proportional to stroke volume but outside this a quadratic relationship is obtained.

Clinical studies in cases of left lower lobe collapse, blockage of descending pulmonary artery and pulmonary embolism show the absence of "lung pulse" in affected zones but its gradual reappearance after successful treatment.

CHANGES IN BLOOD FLOW AND VENTILATION PARAMETERS IN THE LUNG OF THE PIG AFTER LOCAL X-IRRADIATION

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Few reports have been published on the quantitative measurement of late irradiation damage to the lung as indicated by pulmonary function parameters. Using the pig as our experimental model, we have studied the effect of various single doses of 250 kV X rays on a hemi-lung using a similar area of the other lung as a control.

Changes in pulmonary function were evaluated using intravenously injected ^{133}Xe in saline. This allows repeated measurements to be carried out after treatment. This technique has also been demonstrated by other authors to be the most accurate under conditions of poor ventilation, a condition likely to arise following X-irradiation. The accumulation and washout of the radioactive Xenon from areas of interest were measured using externally positioned collimated scintillation detectors.

The maximum accumulation of the radioactive gas in the areas under investigation expresses its regional blood flow to that region. When the subsequent washout curves are reconstructed semi-logarithmically parameters of ventilation can be calculated. In the majority of cases a three-exponential curve was obtained, the first and second exponentials may represent well and less well ventilated alveolae in the same area, while the third exponential, the slowest, represents both the recirculation of the radioactive gas and to a lesser extent the slow release of ^{133}Xe dissolved in the fat.

Changes in pulmonary function have been followed for periods up to two years after irradiation. The preliminary results suggest that there is both impairment of blood flow and ventilation parameters in the irradiated lungs. These changes can occur independently of each other, depending on the irradiation dose.

Proceedings of The British Institute of Radiology

EVALUATION OF A NEW MACROAGGREGATED ALBUMIN KIT FOR LUNG SCANNING AND ITS COMPARISON WITH OTHER AGENTS

By W. J. Hannan, J. D. Simpson, P. Tothill and M. V. Merrick

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Clinical trials have been performed using the prototype of a new macroaggregated albumin (MAA) lung scanning kit (code N101) provided by the Radiochemical Centre, Amersham. Lung views were obtained at various times after injection using a gamma camera. In every case there was an increase in the background radioactivity with an accumulation of technetium in the stomach, and also in the thyroid if this had not been blocked. There was no evidence of uptake of particles in the liver. In some cases where scanning had been delayed, lesions were missed because of the large background activity.

Lung clearance curves were obtained for normally perfused regions by plotting the count-rate in selected regions, corrected for decay, on a log scale against time. Corrections for background radioactivity in the circulation were obtained from an adjacent non-lung region. A single exponential clearance was obtained up to one hour post injection. The average biological half-time from the lungs for seven patients was 54±5 (S.E.M.) minutes. Separate attempts were made to reduce the rate of lung clearance by (a) heating for five minutes at 100°C after reconstituting the macroaggregates with technetium, (b) doubling the stannous oxide content to 0·6 mg per vial, and (c) doubling the autoclave period during the manufacturing procedure. No significant differences in lung clearance rates were obtained between any of the preparations.

For comparison, lung clearance rates were obtained in a similar manner for MAA and microspheres produced by other manufacturers. In each case the lung clearance rate was significantly slower than that of the Radiochemical Centre's MAA.

For each lung agent investigated, clearance information was also obtained from profile scans measured using a shadow shield whole body monitor. The percentage of $^{99}\text{Tc}^{\text{m}}$ from particles in the lungs was calculated by subtracting the contribution to the lung peak due to free technetium in the circulation. This correction was obtained from profile scans of patients who had been given an intravenous injection of $^{99}\text{Tc}^{\text{m}}$ labelled human serum albumin, which remains in the circulation. The average lung retention of $^{99}\text{Tc}^{\text{m}}$ at 24 hours for the Radiochemical Centre's MAA was 19 per cent, while the corresponding values for the other lung agents varied from 27 per cent to 38 per cent. The average whole body retention of $^{99}\text{Tc}^{\text{m}}$ for the Radiochemical Centre's MAA was 67 per cent at 24 hours and the corresponding values for the other agents ranged from 67 per cent to 95 per cent.

The more rapid lung clearance of the Radiochemical Centre's MAA will result in a lower radiation dose to the lungs than the same activity of the other lung agents. However, this will be accompanied by a higher radiation dose to the G.I. tract. The whole body dose for the Radiochemical Centre's MAA is not significantly lower than that for the other lung agents investigated.

THE DISTRIBUTION OF PULOMNARY OEDEMA

By I. H. Kerr

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Alveolar oedema is seen on the chest radiograph as poorly defined patchy shadows of a uniform density with no specific distribution, apart from the "bat's wing" configuration seen sometimes.

Gravity is a dominant factor in pulmonary oedema and fluid will accumulate in the most dependent part of the lung.

Increase in lung water may be appreciated on a chest radiograph without alveolar shadowing. Interstitial oedema can be recognized by septal lines, perihilar haze, and perivascular "cuffing". There is evidence also that upper lobe blood diversion in pulmonary venous hypertension is due to perivascular oedema in the dependent zones.

MEASUREMENTS OF REGIONAL LUNG WATER WITH $H_2{}^{15}O$

By F. Fazio, C. G. MacArthur, C. G. Rhodes, T. Jones and J. M. B. Hughes

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Indicator-dilution techniques are being used for estimating extravascular lung water (ELW) *in vivo*. Using tritiated water as a diffusible indicator, these methods require extensive arterial sampling and time-consuming laboratory procedures for liquid scintillation counting. Besides, they do not provide information on the regional content of ELW (RELW). Regional information can be obtained by using gamma emitting tracers. Using the cyclotron produced ^{15}O labelled water we demonstrated the feasibility of estimating ELW by external counting in the dog (Fazio *et al.*, in press). The technique has now been extended to man. It is relatively non-invasive, requiring only central venous injection of isotopes (^{113}In as a non-diffusible intravascular indicator and $H_2\,{}^{15}O$ as a diffusible indicator) and external recording by means of probes collimated over the chest. The total absorbed radiation dose is 0·3 rad. This technique provides quantitative information on regional blood flow, blood volume, and extravascular water volume in the lungs. In addition, data on RELW per unit of blood volume or per unit of blood flow can be readily obtained.

Seven normal subjects and 11 patients with various heart diseases with little or no radiological evidence of pulmonary oedema have been studied in the supine position. ELW was elevated above the normal range in all but two patients, the increase being more marked at the lung base. This contrasted with normal subjects where the distribution of ELW was uniform from apex to base. In order to distinguish patients from normal subjects the more sensitive indices have been found to be RELW/blood flow and RELW/blood volume.

The technique is suitable for following sequential accumulation of RELW in relation to regional blood flow and volume in patients with acute left heart failure.

REFERENCE

FAZIO, F., JONES, H., RHODES, C. G., JONES, T., and HUGHES, J. M. B. Measurement of total and regional lung water *in vivo*. *Journal of Nuclear Medicine and Biology* (in press).

MEASUREMENT OF LUNG WATER IN SHOCK LUNG AND OTHER CLINICAL STATES

By W. A. Crosbie

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While pulmonary oedema is a common clinical condition the ability to detect, measure and follow changes in the amount of water in the lungs is poor. A method useful in clinical practice is urgently required. The double indicator technique developed by Chinard *et al.* (1962) has recently been applied to experimental states and also in clinical situations. It has been found to measure a proportion of the total mass of water present in the lungs but does not measure water in parts of the lung which are not accessible to the labelled water from the lung vascular compartment. Nevertheless, in the chronic uraemic subject who develops lung oedema, there is good agreement between the clinical/radiological assessment and the amount of water detected by this technique. Patients without any evidence of excess water in their body or lungs have the normal amount of water in the lungs, those with a more than 5 kg gain in body weight have double the normal value and those with severe pulmonary oedema have a threefold increase. It has also been found that patients in the intensive care unit who develop acute respiratory failure also show an increased amount of water in the lungs as shown by this technique. When they improve the amount of water detected decreases. Thus, the double indicator technique can measure water in contact with perfused capillaries in the lungs. But it is an invasive technique; biochemical analysis and access to a computer is necessary. Hence, it is not a clinical tool.

REFERENCE

CHINARD, F. P., EMMS, T., and NOLAN, M. F., 1962. Pulmonary extravascular water volumes from transit and slope date. *Journal of Applied Physiology*, *17*, 179–183.

THE RELATIVE CONTRIBUTION OF THORACIC CAGE AND DIAPHRAGM MOVEMENT TO REGIONAL LUNG FUNCTION

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Regional ventilation and perfusion were studied using ^{133}Xe in two groups of patients (a) ankylosing spondylitis with a fixed thoracic cage (nine patients), and (b) unilateral phrenic paralysis with healthy lungs (five patients).

Ankylosing spondylitis

In comparison with normal subjects, the patients showed a reduction in total lung capacity and the amount of inhaled Xenon reaching the lung apices was also reduced but the distribution of perfused Xenon was normal.

Unilateral phrenic paralysis

All patients showed a reduction in total lung capacity to which the affected side contributed an average of only 37 per cent. There was a decrease in the amount of inhaled Xenon and a lesser decrease in the amount of injected Xenon reaching the lung base on the paralysed side. The distribution in the opposite lung did not differ significantly from that found in normal subjects, although the proportion of inhaled Xenon reaching the lung base was rather less than in the normal group. The washout of injected Xenon was normal except for slight impairment at the lung base on the paralysed side in one patient and at both bases in another.

ANALYSIS OF VENTILATION DISTRIBUTION USING A GAMMA CAMERA

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Measurements of regional ventilation using scintillation probes and ^{133}Xe have been made for 20 years. Recently the gamma camera has been used for this purpose. It has the advantage that the ventilation distribution is given as a two-dimensional image which can be related to the chest radiograph. This can be helpful in the diagnosis of pulmonary embolism (without infarction) in which there is a mis-match between regional perfusion and ventilation. The disadvantages of using the gamma camera for these measurements is its low detection sensitivity compared to probe systems, and the difficulty in obtaining routine lateral images which can be related to segmental anatomy.

Ventilation can be expressed by the regional count-rate following a single total lung capacity of ^{133}Xe, but the wash-out rate of ^{133}Xe, following a rebreathe period, gives a more "physiological" assessment of ventilation in terms of regional turnover of gas. Wash-out studies with ^{133}Xe are complicated by extra-pulmonary radioactivity dissolved in blood and other tissue, and the rather low count-rates obtained from the gamma camera, even when a high sensitivity collimator is used.

Indices of regional ventilation may be computed from the ^{133}Xe wash-out data, but since this is not a single exponential function with respect to time, different methods have been tried to express wash-out as a simple parameter of function.

THE USE OF THE SHORT-LIVED RADIOACTIVE GAS ^{81}Kr^{m} FOR STUDYING REGIONAL VENTILATION: THEORETICAL ASPECTS

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The radionuclide ^{81}Kr^{m} has a half-life of 13 seconds and is the decay product of cyclotron produced ^{81}Rb whose half-life is 4·5 hours. It is possible to elute ^{81}Kr^{m} continuously in the gas phase by passing air over ^{81}Rb bound to a resin column. The continual inhalation of ^{81}Kr^{m} results in the radioactivity in the lungs reaching a steady state which principally represents the balance between the regional arrival of ^{81}Kr^{m}, that is, regional ventilation, and radioactive decay of the tracer. This follows since during resting breathing in adult man ventilatory wash-out of ^{81}Kr^{m} from the lung is secondary to decay of the tracer within the organ. The rapid rate of decay effectively freezes the dynamic component of ventilation in a way analagous to breath holding in the single breath technique for regional ventilation studies. Thus the steady state distribution of ^{81}Kr^{m} in the lungs as recorded by monitoring the emitted 190 keV γ rays with a gamma camera, represents a functional image of regional lung ventilation (Fazio and Jones, 1975). These ventilation images are of high statistical quality and are complementary to those obtained for regional lung blood flow following an intravenous injection of ^{99}Tc^{m} MAA (140 keV). A principal feature in using ^{81}Kr^{m} for ventilation studies is the ability to follow minute by minute changes in the distribution of ventilation. This follows since the short half-life results in a continuous replenishment of the ventilation image. The problems of obtaining quantitative measurements using this method are discussed. Particular reference is made to the ability to complement the ^{81}Kr^{m} ventilation image with a ^{81}Kr^{m} lung blood flow image as obtained by continuously infusing a solution of this tracer intravenously.

REFERENCE

FAZIO, F., and JONES, T., 1975. Assessment of regional ventilation by continuous inhalation of radioactive krypton-81 m. *British Medical Journal*, *3*, 673–676.

THE USE OF SHORT-LIVED RADIOACTIVE GAS $^{81}\text{Kr}^{m}$ STUDYING REGIONAL VENTILATION: CLINICAL APPLICATIONS

By J. P. Lavender and F. Fazio

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The theoretical basis of using the short-lived gas $^{81}\text{Kr}^{m}$ in steady state to produce a picture of a regional ventilation is outlined in the previous paper. The method can be used both as a physiological or clinical tool. Thus, in the normal subject, pictures can be taken within a few minutes of each other to show different patterns of ventilation. The pattern with a subject in the erect position can be shown to redistribute on changing to a lying or inverted position. Similarly, regional lung perfusion can also be shown by infusing Krypton intravenously to a steady state and again sequences of pictures illustrate changes in regional perfusion which are dependent on gravity.

The method which has been used in some 200 patient examinations involves the use of Technetium labelled microspheres to assess regional perfusion and Krypton is used for ventilation scanning. This allows multiple views of the lung representing ventilation and perfusion which are taken in the same position and all during tidal respiration. Patients with acute bronchitis and bronchospasm may show large areas of reduced ventilation with a reversal to a normal pattern after treatment. These changes are not necessarily reflected in the radiographs which may remain normal throughout.

Pulmonary embolic disease is characterized by segmental defects of perfusion with normal or near normal patterns of ventilation. Lateral views of ventilation and perfusion are particularly valuable in giving a clear picture of segmental anatomy. Chronic parenchymal lung disease shows complex patterns of perfusion and ventilation defects. Although these usually superimpose, mis-matching may occur. Bronchogenic carcinoma may be associated with defects of both perfusion and ventilation, not predictable from chest radiographs. Krypton ventilation scanning in such patients allows changes following radiotherapy to be documented and can be used as a pre-operative surgical assessment of regional lung function. Quantitation can be applied to this data to give ventilatory exchange of the two lungs separately.

VENTILATION STUDIES IN INFANTS

By S. Godfrey

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The importance of radio-isotopic gas studies in infants and small children lies in the fact that it has provided us with the only method of studying regional and total lung function at an age when other forms of lung function testing are impractical and when many pulmonary conditions require evaluation. The technique which has been developed requires no active co-operation from the child, causes no distress, and presents no significant radiation hazard.

The child lies supine over a gamma camera under light sedation if necessary with a catheter passed through the nose to the nasopharynx for the inhalation study and a peripheral venous line in place for the perfusion study. In the former study a bolus of ^{13}N (0·3 mCi/kg up to 2 mCi) is delivered at end expiration and inhaled on the next breath with subsequent washout. In the perfusion study a similar bolus of ^{13}N dissolved in saline is delivered intravenously. In both cases the arrival and wash-out of activity is monitored by the gamma camera linked to a computer system which enables corrected regional activity-time plots to be obtained.

Studies have been carried out in over 40 infants and children using this technique and have proved its clinical value beyond question.

PHYSIOLOGICAL DETERMINANTS OF VENTILATION DISTRIBUTION

By J. M. B. Hughes

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Local ventilation is related to the inspiratory and expiratory forces applied to the pleural surface locally (ΔP), local compliance and airway resistance and the overall flow rate and tidal volume (Hughes *et al.*, 1972). During normal breathing the flow rate will be set by the tidal volume and the inspiratory and expiratory duration. For the same ΔP, units with a high local resistance will receive proportionately less ventilation when flow rates are high and inspiratory duration short. When flow rates are low and inspiratory time long ventilation will be distributed more according to regional compliance. The pattern of filling, as opposed to ventilation, depends on the local time constant (resistance × compliance). In erect normal subjects the upper zones of the lung are less well ventilated at low flow rates because the alveoli have a higher resting volume than those at the base, and are consequently stiffer. At fast flow rates apical ventilation exceeds basal either because the distribution of ΔP has changed or because the airways to the relatively over-expanded upper zones are wider.

With radioactive gases there are basically two types of measurement: (a) single breath, (b) wash-in or wash-out. Inter-zonal differences should be detected by the former but clearance techniques (using gases of lower solubility than xenon) are needed to detect subtle intra-regional defects of ventilation. Extra information about local mechanics can be obtained by inhaling a radioactive gas bolus at different flow rates. Local ventilation-perfusion mismatching can be studied from the lung clearance of insoluble radioisotopes injected intravenously.

REFERENCE

HUGHES, J. M. B., GRANT, B. J. B., GREENE, R. E., ILIFF, L.D., and MILIC-EMILI, J., 1972. Inspiratory flow rate and ventilation distribution in normal subjects and in simple chronic bronchitis. *Clinical Science*, *43*, 583–595.

REGIONAL VENTILATION IN ASBESTOS WORKERS

By N. N. Stanley*

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Regional ventilation was assessed in eight healthy subjects and in 14 pipe-coverers with a prolonged (>20 years) occupational exposure to asbestos dust. Simple lung function tests has shown minimal impairment in overall ventilatory function in seven of the workers; four had interstitial fibrosis and six had pleural fibrosis evident at the lung bases on chest radiography.

Each subject was studied in the seated position. The radioactivity in both lungs was recorded by a gamma camera during the wash-out of ^{133}Xe which had been breathed to equilibrium in a closed circuit. Activity-time plots were constructed using data from upper, middle and lower lung zones. In healthy subjects the first 70 per cent of wash-out was always fastest in the lower zones. In two of the asbestos workers, however, the activity declined more slowly throughout the whole of wash-out in the lower compared with the middle zones. In ten others the fall in activity was initially fastest in the lower zones but soon became slower than in the middle zones, which caused a cross-over of the lower and middle zone curves before wash-out was 70 per cent complete. These findings are consistent with hypoventilation of some lung units within the lower zones and analysis of ^{133}Xe wash-out curves may provide a sensitive method for the early detection of pulmonary asbestosis.

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EVALUATION OF REGIONAL LUNG FUNCTION USING THE OHIO-NUCLEAR REGIONAL PULMONARY FUNCTION ANALYZER

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The Ohio-Nuclear Regional Pulmonary Function Analyzer is a commercially produced multidetector system for determining regional lung function using ^{133}Xe. Results from the Analyzer have been compared with those obtained using other techniques, both in normal subjects and in patients with cardiopulmonary disorders.

In 28 normal subjects and 18 patients the Analyzer gave consistently lower values for vital capacity than those obtained by spirometry ($Y=0{\cdot}642\ X+0{\cdot}602$, $r=0{\cdot}70$; where X = spirometer, Y = Analyzer) and higher values for residual volume than those measured by the helium dilution technique ($Y=0{\cdot}962\ X+0{\cdot}715$, $r=0{\cdot}78$; where X = helium dilution, Y = Analyzer).

In 10 normal subjects and 11 patients, regional lung function was measured with the Analyzer and a Nuclear Enterprises Mark 5 gamma camera. The regional distribution of radioactivity within the lung following rebreathing of a xenon/air mixture from a closed-circuit spirometer system showed the regional distribution of lung volume. Ventilation distribution was measured using the bolus technique of Milic-Emili *et al.* (1966) and purfusion distribution using the method of Anthonisen and Milic-Emili (1966). The results from the six regions viewed by the Analyzer were compared with equivalent areas of the gamma camera field. In normal subjects the two detector systems gave similar regional distributions of lung volume ($Y=0{\cdot}981\ X+0{\cdot}043$, $r=0{\cdot}86$; where X = gamma camera, Y = Analyzer); ventilation ($Y=0{\cdot}906\ X+0{\cdot}110$, $r=0{\cdot}68$); and perfusion ($Y=0{\cdot}711\ X+0{\cdot}245$, $r=0{\cdot}74$). In patients, however, there were more discrepancies between the gamma camera and the Analyzer values (distribution of lung volume, $Y=0{\cdot}688\ X+0{\cdot}350$, $r=0{\cdot}63$; ventilation, $Y=0{\cdot}605\ X+0{\cdot}401$, $r=0{\cdot}54$; perfusion, $Y=0{\cdot}545\ X+0{\cdot}411$, $r=0{\cdot}51$). These differences may be attributable to the limited sensitivity to regional abnormalities of the six counter system of the Analyzer.

REFERENCES

MILIC-EMILI, J., HENDERSON, J. A. M., DOLOVITCH, M. B., TROP, D., and KANEKO, K., 1966. Regional distribution of inspired gas in the lung. *Journal of Applied Physiology*, *21*, 749–759.

ANTHONISEN, N. R., and MILIC-EMILI, J., 1966. Distribution of pulmonary perfusion in erect man. *Journal of Applied Physiology*, *21*, 760–766.

AN INTEGRATED ^{133}XE REGIONAL PULMONARY FUNCTION ANALYZER

By R. G. Rawbone

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An integrated system for diagnostic quantitative, static and dynamic regional pulmonary function analysis—both ventilation and perfusion—has recently been developed by Ohio Nuclear. This Analyzer utilizes the isotope ^{133}Xe with detection of intrapulmonary counts by six externally positioned scintillation detectors. The Analyzer consists of three units:

(1) A mobile console provides the operating controls, digital data display and contains Xenon delivery and rebreathe systems, gas trap and computing electronics.
(2) A stand supporting the adjustable detector array and patient chair.
(3) A gas mixing and storage system.

A single technician may operate the Analyzer and the whole procedure from meeting the patient to presentation of analyzed and reported results can be performed in less than 30 minutes.

By calibrating the system, including the patient, at the commencement of a study, lung volumes can be obtained in absolute terms. The results displayed are: regional vital capacity, regional equilibration data after rebreathing, differential FER, differential residual volume and wash-out data. Following an intravenous injection of ^{133}Xe, regional perfusion data can be obtained. Distribution indices independent of lung volume may be derived.

The results from 100 studies, including 52 ventilation studies and 20 perfusion studies in normal subjects will be presented. These are shown to be comparable to other published series. Case reports illustrating the clinical application of the Analyzer will be demonstrated.

1976, *British Journal of Radiology*, *49*, 475–476 MAY 1976

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

SPOILT FILMS IN X-RAY DEPARTMENTS AND RADIATION EXPOSURE TO THE PUBLIC FROM MEDICAL RADIOLOGY

Whilst all exposure of the public to ionizing radiation has been a matter of increasing public concern in recent years, and medical radiology contributes the largest amount of man-made exposure (approximately one-quarter of natural background radiation), such medical exposure must be considered separately from all other sources of radiation exposure to the public as it is undertaken *specifically to benefit the individual exposed.* It is nonetheless proper to inquire whether in current radiological practice reductions can be made in radiation exposure to the population—and at what cost? Unsupported allegations have been made that the need to retake spoilt X-ray films or films of inadequate quality adds significantly to the radiation dose received by the population from medical radiology. Under the aegis of the Radiation Protection Committee of the British Institute of Radiology, a survey was carried out during January and February 1975 of the numbers and causes of spoilt X-ray films in four X-ray departments which represent typical examples of the four major types of hospitals, *viz.* teaching hospital, district general hospital (with school of radiography), accident and emergency service, and private nursing home. The participating hospitals and the consultant radiologists and/or superintendent radiographers who collaborated in the collection of these data are shown in Table I. For a period of either one month or two months, *all* films taken in each department were reviewed. The data are summarized in Table II. In all four types of X-ray departments, the majority of films retaken were required because of exposure faults—particularly in films taken with portable radiographic equipment. The next most common cause of failure was positioning faults, which included selection of the wrong beam-limiting cone or diaphragm setting, mis-positioning of the cassette relative to the X-ray beam, failure to push home the cassette tray, etc. The proportion of films which were rejected as being non-contributory to the examination was significant only in the teaching hospital in which a higher proportion of complex procedures were undertaken. Known persistent or recurrent machine faults in the district general hospital department reflected the

TABLE I

Type of hospital	Name	Principal collaborators in survey
Teaching	Churchill Hospital, Oxford	Dr. F. W. Wright, Consultant Radiologist Miss D. M. Haigh, Superintendent Radiographer
District general	Horton General Hospital, Banbury, Oxon.	Dr. J. L. Boldero, Consultant Radiologist Mr. R. Pinnock, Superintendent Radiographer
Accident/emergency	Coventry and Warwickshire Hospital, Coventry	Miss D. N. Chesney, Group Superintendent Radiographer
Private nursing home	The Acland Home, Oxford	Dr. E. W. L. Fletcher, Consultant Radiologist Mrs. P. M. Burns, Superintendent Radiographer

TABLE II

Type of hospital	Number of examinations sampled	Average number of examinations per patient	Number of films used	Average number of films per examination	Number of spoilt films	Number of patients with spoilt films	Major causes of spoilt films
Teaching	4,198	1·8	17,500	4·2	864 (4·9%)	518 (12·4%)	1. Exposure fault (47%) 2. Positioning fault (25%) 3. Film non-contributory to examination (11%)
District general	1,896	1·3	4,995	2·6	397 (8·0%)	327 (21·8%)	1. Exposure fault (33%) 2. Positioning fault (32%) 3. Machine fault (14%)†
Accident/ emergency	3,951	1·2	7,366	1·9	439 (6·0%)	*(13·6%)	1. Exposure fault 2. — 3. —
Private nursing home	174	1·2	498	2·9	15 (3·0%)	13 (9·1%)	1. Exposure fault (87%) 2. Positioning fault (13%)
Total	10,219	1·5	30,359	3·0	1,715 (5·7%)	* (18·0%)	

*Calculated value from average number of examinations per patient.
†Machine in one X-ray room was persistently faulty during period of survey.

pressure of work which required continued use of a machine known to be troublesome, but machine faults did not make a large contribution overall in causing X-ray films to be retaken. Patient movement and non-co-operation were of only relatively minor importance in causing X-ray films to be spoilt.

The predominance of exposure faults in causing films to be retaken prompted an enquiry into the cost of providing automatic exposure control in new X-ray apparatus; depending upon the degree of sophistication required, this would add *circa* 17–30 per cent to the cost of a complete new installation. Making similar provisions for at least some existing X-ray machines is possible, but at *circa* £2,000 per machine it is clearly not economically feasible. Providing automatic limitation of X-ray field size and cassette line-up for over-table tubes in new apparatus would add approximately 12–15 per cent to its cost, and such provisions are already made in all new undercouch systems used with image-intensifiers. No automatic control of either exposure or position is possible for portable X-ray generators and these are the source of a high proportion of spoilt films in current practice—however, portable X-ray generators are normally used only in the worst clinical situations with very ill patients whose prognosis may be very poor indeed.

In summary, if the results of this survey are truly typical of radiographic practice in the U.K. approximately *one patient in six* who undergoes X-ray examination has at least one film spoilt and retaken. Overall, however, this results in only *circa* 5–6 per cent increase in the population exposure to radiation which occurs as a result of medical radiography, a very small figure indeed. Providing automatic controls of exposure and field size on all new X-ray machines, which could thus only reduce population exposure by *less than 5 per cent* of that due to medical radiography would add, respectively, up to 30 per cent and 15 per cent to their capital cost. The results of this survey are similar to those of Koga (1968) who surveyed spoilt films in five large Japanese hospitals and found an overall retake rate of *circa* 2 per cent, and ascribed more than 40 per cent of these to "radiographer errors", approximately 20 per cent to "machine failures".

Continuation of the high standard of U.K. radiographic practice found in our survey cannot be taken for granted, and will result only from maintaining present levels of training and supervision; for the present it remains a source of justifiable pride. We acknowledge our thanks to all the radiographers in the four departments, who participated enthusiastically in this study.

Yours, etc.,
R. J. BERRY,
Chairman
R. OLIVER,*
Secretary

Radiation Protection Committee,
British Institute of Radiology.

REFERENCE

KOGA, S., 1968. Extra exposure to the patient by X-ray examination (Reduction of patient dose in X-ray fluoroscopy and radiography. 3rd Report). *Nippon Acta Radiologica*, *27*, 105–109.

*Deceased March 6, 1976.

THE EDITOR—SIR,

MUST RADIOLOGISTS DO ALL THE REPORTING?

The concept of clinical assistance raised in your editorial of July, consequent upon Dr. Emrys-Roberts' letter, may be new to some radiologists. In fact the idea is not new, and I have been involved as long ago as 1963 in suggesting their value and use to the Faculty of Radiologists.

I personally established such a post in the mid-Cheshire group of hospitals, and here in Aberdeen we have a G.P. clinical assistant working in the teaching hospital department. In my experience the system works excellently and has much to commend it.

To those who oppose the idea, I would remind them that the future existence of our speciality is gravely threatened by high emigration, poor recruitment and the intrusion of non-medical practitioners of physical crafts.

We need, therefore, to encourage our colleagues to join in providing a service of value equally to both general and hospital practitioners and so ensuring our speciality's future existence.

The College of Radiologists' suggestion that all radiology is consultant work is patently unrealistic; rather let us put our house in order in respect of a career and training structure that welcomes clinical assistants into our speciality as did the Faculty of Anaesthetists 24 years ago.

Yours, etc.,
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THE EDITOR—SIR,

THE NEW SPECIAL NAMES OF SI UNITS IN THE FIELD OF IONIZING RADIATIONS

At the meeting of the International Commission on Radiation Units and Measurements (I.C.R.U.) in July, 1974, the extensive worldwide response to the previous correspondence on SI units (Lidén, 1973; 1974) was discussed in considerable detail. A statement on SI units was then prepared and sent to the International Committee of Weights and Measures, C.I.P.M. for consideration. In this statement the I.C.R.U. recommended the adoption of special names for the SI unit the joule per kilogram, J/kg, when applied to absorbed dose and related quantities, and for the SI unit the reciprocal second, s^{-1}, when applied to the quantity activity as a measure of the rate of spontaneous nuclear transformation of radioactive nuclides. The I.C.R.U. statement was also discussed at the I.A.E.A. symposium on Advances in Biomedical Dosimetry, March 10–14, 1975 (Lidén, 1975). The C.I.P.M. treated the I.C.R.U. proposals with expedience and drafted two resolutions for consideration by the 15th General Conference of Weights and Measures, C.G.P.M. at its meeting in May–June, 1975. At this meeting, which celebrated the 100-year anniversary of the Meter Convention, the C.G.P.M. adopted the following resolutions:

"Resolution H 1

The Fifteenth Conférence Générale des Poids et Mesures,
—owing to the urgency, expressed by the International Commission on Radiation Units and Measurements (ICRU), to extend the use of the International System of Units to research work and applications in radiology,
—owing to the necessity of making the use of units as simple as possible for non-specialists,
—taking into account the seriousness of the risk of errors in therapy,
ADOPTS the following special name of SI unit for activity: the becquerel, symbol Bq, equal to the second to the power minus one.

Resolution H 2

The Fifteenth Conférence Générale des Poids et Mesures,
—owing to the urgency, expressed by the International Commission on Radiation Units and Measurements (ICRU), to extend the use of the International System of Units to research work and applications in radiology,

—owing to the necessity of making the use of units as simple as possible for non-specialists,

—taking into account the seriousness of the risk of errors in therapy,

ADOPTS the following special name of SI unit for ionizing radiations:

the gray, symbol Gy, equal to the joule per kilogram. Explanatory note.—The gray is the SI unit of absorbed dose. The gray can also be used with other physical quantities expressed in joules per kilogram provided these quantities belong to the field of ionizing radiations."

Thus the SI unit the joule per kilogram when used for ionizing radiation (absorbed dose, kerma, specific energy imparted, etc.) is given the name *gray* with the symbol *Gy*: 1 Gy = 100 rad = 1 J/kg. And the SI unit the reciprocal second (one per second) for activity is given the name *becquerel*, symbol *Bq*. $1\ \text{Bq} = 1\ \text{s}^{-1} \approx 2{\cdot}703 \times 10^{-11}\ \text{Ci}$.

Antoine Henri Becquerel (1852–1908) discovered radioactivity in 1896 ("rayons de Becquerel") and was given the Nobel Prize in physics in 1903 together with Marie and Pierre Curie.

Louis Harold Gray (1905–65) made one of the most fundamental contributions to radiation dosimetry, the principle now known as the Bragg-Gray Principle.

The I.C.R.U. did not recommend to the International Committee of Weights and Measures that a special name be given to the SI unit of exposure to replace the currently used röntgen.

The I.C.R.U. now recommends that the special units the rad, the röntgen and the curie be gradually abandoned over a period not less than about ten years and replaced by the SI units the gray (Gy) the coulomb per kilogram (C/kg) and the becquerel (Bq), respectively. It is desirable that preparatory steps be taken as soon as possible by various national and international bodies in order to facilitate a smooth, safe and efficient transition.

In its report *Supplement to I.C.R.U. Report 19, Dose Equivalent* (I.C.R.U., 1973) the I.C.R.U. published its decision that the physical dimension of the quantity *dose equivalent* should be the same as for absorbed dose. From the radiation protection point of view the availability of a proper set of quantities and units in this field is of paramount importance. The formulation (for selection) of a suitable unit for dose equivalent is therefore a special problem which will be thoroughly discussed by I.C.R.U.

On behalf of the International Commission on Radiation Units and Measurements:

Yours, etc.,
H. O. WYCKOFF,
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REFERENCES

LIDÉN, K., 1973. SI units in radiology and radiation measurement. *British Journal of Radiology*, *46*, 561–562.

LIDÉN, K., 1974. Special radiation units and/or SI units? *British Journal of Radiology*, *47*, 295.

LIDÉN, K., 1975. SI Units in biomedical dosimetry. In *Biomedical dosimetry*, I.A.E.A., Vienna, p. 451–461.

INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS, 1973. *Dose Equivalent, Supplement to Report I.C.R.U. 19* (I.C.R.U., Washington, D.C.).

THE EDITOR—SIR,

THE INTRODUCTION OF SI UNITS INTO THE RADIOLOGICAL SCIENCES

Some of us have watched the pathologists introducing SI units into their laboratories with a certain fellow-feeling, knowing that our turn was soon to come.

One must applaud the concept of a unified system; it is a pity that it has to be quite so rigid. One desirable attribute of a unit is that it should be of a convenient size, and the fact is that the new unit of activity, the becquerel, is very much too small.

A modest tracer dose will already be in the mega range; a therapeutic dose of radioiodine will be expressed in gigabq. and a large cobalt unit will have a source whose activity is in the hundreds of terabq.

I would suggest that the new unit is at least one million times too small—it is as if, after metrication, road signs were to express distances in millimetres.

In spite of our good resolutions I cannot see anyone greeting the newcomer with any great enthusiasm.

Yours, etc.,
J. P. NICHOLSON.

Physics Department,
Westminster Hospital,
London, S.W.1.

REFERENCE

BOAG, J. W., and BINKS, C., 1976. The introduction of SI units into the radiological sciences. *British Institute of Radiology Bulletin*, *1*, 6.

THE EDITOR—SIR,

FOCAL SPOT SIZE

Measurement of the focal spot size of diagnostic X-ray tubes is a subject which has generated many papers within the last few years and seems likely to provide the basis of many more in the years to come. The recent contribution by Robinson and Grimshaw (1975) is open to the criticism that it equates the "actual" focal spot size as measured by a pinhole method with the "equivalent" (Milne, 1974) size estimated with a resolution pattern. Whilst it cannot be disputed that the limiting resolution of a radiographic system is a very useful figure for comparing system performance, using this limiting resolution to calculate the size of the idealized uniformly emissive focal spot with the equivalent limiting resolution can be very misleading. Perhaps it is time to drop the concept of focal spot size and substitute that of a spot with a specified minimum resolution under specified conditions.

Yours, etc.,
G. WATERS.

187 Headstone Lane,
Harrow,
Middlesex HA2 6LX.

REFERENCE

MILNE, E. N. C., 1974. Characterising focal spot problems. *Radiology*, *111*, 483–486.

ROBINSON, A., and GRIMSHAW, G. M., 1975. Measurement of the focal spot size of diagnostic X-ray tubes—a comparison of pinhole and resolution methods. *British Journal of Radiology*, *48*, 572–580.

1976, *British Journal of Radiology*, *49*, 478

Correspondence

THE EDITOR—SIR,

ULTRASOUND SCANNING IN A RADIOTHERAPY DEPARTMENT

Rapid strides have been made in the proper utilization of ultrasound pulse-echo systems, and B-scanning is now an accepted technique in diagnostic radiology and obstetrics (Wells, 1972). These non-invasive methods are particularly successful in imaging the outlines of internal organs, tumours and cysts in cross-sectional planes, without recourse to contrast media.

Apart from its use by diagnostic radiologists in the detection and staging of tumours, ultrasound scanning appears to offer particular advantages to the radiotherapist in treatment field planning, although this application has so far not been much developed. As confirmed by the reports of some pioneers in the field (Brascho, 1974), the following merits are almost self-evident: tumour, organ and body outlines are visualized, with the patient usually in the treatment position, sufficiently accurate for measurement and field planning, and for verification of the precision of the siting of treatment fields. In particular, the study of scans in a number of parallel planes can provide data for planning optimum dose distribution in three dimensions. Moreover, the safety and high patient-acceptability of the scanning technique allows repeated re-assessment of tumour morphology with consequent early modification of the treatment régime.

At this hospital it has been possible for radiotherapists to obtain direct access to a NE4102 Diasonograph, supplied by the D.H.S.S. for an instrumental development programme in the Department of Medical Physics, without interference in the routine scanning for radiology and obstetrics. Already more than 300 patients undergoing radiotherapy treatment have been scanned, and the technique has proved invaluable in the following contexts:

(1) *Chest wall scanning*, to confirm that the radiotherapy field adequately covers the involved region but avoids, as much as possible, the underlying lung, is useful for planning the treatment of pleural tumours and in the handling of post-mastectomy chest-wall sterilization. We also feel that we are visualizing, with some accuracy, enlargement of the internal mammary nodes. In our experience, water-bath scanning techniques are necessary for accurate results.

(2) *Bladder scanning* to estimate the extent of the tumour within the bladder, its penetration through the bladder wall and its extension through the pelvis allows planning of radiotherapy treatment to all the tumour, but avoiding damage to the rectum. To simulate fully the treatment situation, patients are scanned with an evacuated bladder. Scanning thus also checks the adequacy of bladder emptying.

(3) *Scanning of retroperitoneal tumours* for accurate planning of radiotherapy treatment facilitates avoiding damage to the kidneys and gut. The response of such tumours to radiotherapy or cytotoxic chemotherapy is often rapid and easily checked. The patient is usually in the prone position, and scanned through the back to avoid the sonically impenetrable gut.

(4) *Scanning of tumours* such as soft-tissue sarcomata, thyroid, prostate and ovarian carcinomata and skin tumours ensures accurate treatment planning, and allows subsequent assessment of the results.

(5) *To obtain patient outline*, tumour and organ positional information for calculation of dose distribution. Developments are in hand for providing these data on-line from the scanner to the dose calculation computer.

In certain cases, heavy reliance is now made on the information from ultrasound scanning since more conventional investigation would not allow imaging of the tumour-affected area in the treatment planes. On occasions carefully planned treatments based on conventional planning procedures have had to be modified on the strength of subsequent ultrasound scans which revealed inadequate cover of the tumour or non-optimal treatment field positioning.

It would seem advisable that all radiotherapy departments should acquire the necessary expertise and personnel to ensure that access to ultrasound scanning systems is easily available, both to increase the accuracy of defining the tumour-bearing area for treatment planning, and to avoid other methods of investigation involving especially invasive techniques, as these are often time-consuming, costly, unpleasant for the patient and occasionally hazardous. Furthermore, we would stress the personal involvement in the scanning of both the radiotherapist, as an aid to him in treatment planning, and the physicist, to exploit the capabilities of the scanning machinery to the full.

It is therefore suggested that ultrasound scanning equipment should be conveniently accessible to the radiotherapy patients and be associated with other planning facilities. It is also felt that the difficulties and pitfalls in using this scanning modality may be easily overcome if the radiotherapist is given the opportunity during training to learn and practice the technique.

Yours, etc.,
P. BADCOCK.

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Hammersmith Hospital,
Du Cane Road,
London W12 0HS.

S. LEEMAN.

Department of Medical Physics,
Royal Postgraduate Medical School,
Hammersmith Hospital.

ACKNOWLEDGMENTS

We are grateful to Professor R. Oliver and Dr. R. Morrison for their encouragement and advice. Dr. S. Leeman is in receipt of a Wellcome Fellowship.

REFERENCES

BRASCHO, D. J., 1974. *Ultrasound in Radiation Therapy Planning* (Unirad Corporation, Denver).

WELLS, P. N. T. (Ed.), 1972. *Ultrasonics in Clinical Diagnosis* (Churchill Livingstone, London).

THE EDITOR—SIR,

TIME FOR A REALIGNMENT OF PROFESSIONAL ASSOCIATIONS OF RADIOLOGISTS?

Many of those who read the statement of co-operation issued by the British Institute of Radiology and the newly promoted Royal College of Radiologists will have wondered why the two organizations have not simply been amalgamated. Certainly the statement detailed an impressive list of identical roles. Both organizations aim to continue to encourage the practice of diagnostic and therapeutic radiology, ultrasound and nuclear medicine. Both associations will continue to promote meetings and lectures, and each emphasizes the importance of meetings with those working in other disciplines. Together they are recognized as authorities competent to offer advice on matters relating to radiological practice. There is some hope that they will share the same premises, particularly for the use of the editorial staff of the respective journals. The two associations assured their members of continued and increasing co-operation between related Committees of the two organizations.

There are of course significant dissimilarities. The Royal College is charged with the supervision and organization of postgraduate training and qualification in radiology. It assumes the responsibility for negotiating with the Department of Health on professional matters. However, these functions would not be disturbed by a merger. The British Institute provides a forum in which those interested in the medical use of radiology, whether medical or non-medical, may meet on equal terms. An amalgamation would exclude non-medical members, but of course an equivalent forum could be provided by meetings between the combined association and a special section of an established society or a new non-medical group formed for the purpose.

A federation of the two organizations representing those doctors concerned with the medical use of radiation may be feasible. Its desirability is another matter. It would perpetuate one of the present anomalies in both the Royal College and the Institute. The continued close association of diagnostic and therapeutic radiology is an anachronism. Today the diagnostic radiologist has more in common with the other diagnostic disciplines in pathology than he has with the radiotherapist. The radiotherapist, concentrating on oncology, has greater liaison with other medical and surgical therapists than he has with the diagnostic radiologist. There are few radiotherapy articles in *Clinical Radiology* and the *British Journal of Radiology* which are of special interest to the pracising diagnostic radiologist, and I suspect, vice versa. Witness the small number of articles written jointly by therapists and diagnosticians. Witness the difficulty in finding new topics for discussions at combined sessions at radiological meetings. The association of diagnostic and therapeutic radiologists is no more logical than an association between otorhinolaryngologists and ultrasonologists, though it has one justification. It is a small step in the direction of an amalgamation of all the Colleges. This desirable arrangement, which has been achieved in part in Canada, would help to develop much greater professional cohesion, break down some of the interspecialty barriers, and encourage a more uniform standard of specialist training and examination.

The logical solution, that there should be a separation of the two disciplines, has the merit of economy. At present both therapists and diagnosticians are obliged to support facilities, meetings and journals, only a proportion of which are relevant to their work. The recent dramatic increase in the annual subscription to the Royal College of Radiology will have led many to ask themselves if they will continue to subscribe to both organizations. Doubtless there will be arguments raised in favour of maintaining the status quo, and perhaps there are too many influential parties with an interest in avoiding change. Perhaps the only practical change is to reorganize the present Royal College into two separate faculties, for therapy and diagnosis. The most substantial objection to the realignment lies in the demise of the Institute. Contrary to expectation, the older Institute is characterized by youthful vigour and relevance to clinical practice, and if this vigour were lost in the realignment it would be sufficient to condemn any change.

In summary, the logical conclusion of the statement of co-operation between the British Institute of Radiology and the Royal College of Radiologists is that they should amalgamate. This fusion would clear the way for a division of the Royal College into diagnostic and therapeutic faculties. The new faculties should be characterized by the energy and practicality presently exhibited by the Institute.

Yours, etc.,
M. J. BRINDLE.

West Norfolk and King's Lynn
General Hospital,
London Road,
King's Lynn,
Norfolk PE30 5QD.

(The editors invited Dr. Brindle to write on this subject.

THE EDITOR—SIR,

ARDRAN/CROOKS PENETRAMETER CASSETTE—NECESSITY FOR RE-CALIBRATION

We have frequently been asked if the penetrameter cassette described by us (1968) requires frequent re-calibration. When this cassette was first designed it was our opinion that calcium tungstate intensifying screens did not alter in speed with time or use unless obviously worn, abraided, stained or dirty; we still hold this view. Our first cassettes have now been in use for ten years and have not changed their calibration with the exception of one which became incorrect at one particular copper reference number (CRN); this was thought to be due to local dirt and when thoroughly cleaned the defect disappeared.

We have, however, over recent years, become aware of some five or more cassettes made by others in which the calibration has been or has become incorrect. In each case they have given a low reading for kilovoltage compared with the original calibration, particularly in the higher ranges. We have checked one such cassette believed to have been made in 1972 or early 1973 and which we found to give low readings from 80 to 130 kV constant potential; the discrepancy gradually increased above 80 kV and the reading was 8–10 kV low at 130. Recalibration was carried out in March 1974 without the cassette having been used since it was first calibrated. This cassette has only been occasionally used since but a re-check of its calibration in August 1975 indicated that the low readings now started at about 60 kV and increased up to 130 kV at which point the reading was still 8–10 kV too low.

This latter cassette and most if not all the cassettes whose calibrations have changed with time used Ilford high definition intensifying screens which were dyed yellow. Our cassettes were made with Ilford high definition screens which were not dyed yellow and were virtually indistinguishable in appearance from Ilford fast tungstate screens which have also been used in the construction of cassettes. Our high definition screens were cut from a pair which were surplus old stock and comparatively unused. We therefore believe that the changes in calibration are associated with the yellow dyed screens and the phenomenon could be explained if the dye, used to reduce internal light scatter, faded and thus allowed the screens to become faster with time. We have some evidence that these screens may stabilize after two to three years. The increase in speed which might account for this phenomenon would be approximately 10 per cent; this would not normally be significant during their lifetime. It is obvious that whatever type of intensifying screens are used it will be advisable to see that they are not exposed to light more than is absolutely necessary.

We have discussed this problem with Mr. A. H. Waller, X-ray Product Development Division, Ilford Ltd., Brentwood, Essex and he has indicated that he would be willing to supply slow screens for penetrameter cassette construction which do not include a yellow dye. We are grateful for his help.

Yours, etc.,
G. M. ARDRAN,
H. E. CROOKS.

Environmental and Medical Sciences
Division,
A.E.R.E. Harwell, and The Nuffield
Institute for Medical Research,
University of Oxford.

REFERENCES

ARDRAN, G. M., and CROOKS, H. E., 1968. Checking diagnostic X-ray beam quality. *British Journal of Radiology*, *41*, 193–198.

1976, *British Journal of Radiology*, *49*, 480–481

Forthcoming events and other notices

The editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meetings announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

THE USE OF HYPERTHERMIA AND NON-IONIZING RADIATION IN THE TREATMENT OF CANCER, May 21, 1976

This meeting to be held at the British Institute of Radiology, Institute House, 32 Welbeck Street, London W1M 7PG. Further information from the General Secretary.

POSTGRADUATE COURSE IN TOMOGRAPHY OF THE TEMPORAL BONE

To be held in Copenhagen, June 3–4, 1976. The course is sponsored by the I.C.R., the A.E.R. and the Scandinavian Association of Radiologists.

For further information and registration, please contact Dr. Paul E. Andersen, Department of Radiology, University Hospital, 5000 Odense, Denmark.

HEALTH PHYSICS SUMMER SCHOOL

The 17th annual Summer School in Health Physics (Radiation Protection) will be held at Imperial College from June 21 to July 2, 1976.

Enquiries to Dr. H. D. Evans, Department, of Chemical Engineering, Imperial College, London SW7 2AZ.

BREAST: NON-CANCEROUS DISEASES

To be held in Strasbourg, France, June 30–July 3, 1976. The 4th International symposium on Senology, under the auspices of the European Association of Radiology.

The symposium will be preceded by postgraduate teach-ins, on June 28, 29, ultrasonography (by Société Française d'Echographie) on June 29, thermology (European Thermographic Association) and on June 29, xerography.

Apart from the postgraduate teach-ins, there will be simultaneous translation in the official languages of the symposium – English, French and German.

Further information from Symposium Sénologie 1976, Professor Charles Gros, Palais des Congrès, 67000 Strasbourg, France.

COMPUTERS IN RADIOTHERAPY IN EUROPE

It is proposed to hold a Workshop at IAEA, Vienna, on July 5–10, 1976, organized by the Groupe Informatique, A.E.R. with the support of the European Association of Radiology. The aim will be to establish the contribution that the computer makes at the clinical level in the fields of dose computation, clinical records, radiobiology, etc., and to determine future development.

Further information from Dr. D. N. Edwards, Clinical Research Unit, Mersey Regional Centre for Radiotherapy and Oncology, Clatterbridge Hospital, Bebington, Wirral, Merseyside L63 4JY, U.K.; or Dr. T. Moller, Radioterapikliniken, Lasarettet, S-221 85 Lund, Sweden.

FIRST MEETING OF THE WORLD FEDERATION OF ULTRASOUND IN MEDICINE AND BIOLOGY

This meeting, to be held August 3–7, 1976 in San Francisco is the third world congress on ultrasonics in medicine.

Reduced registration fees are payable by members of the international sub-group of the British Medical Ultrasonics Group.

Further information from: 1st W.F.U.M.B., PO Box 25606, Oklahoma City, Oklahoma 73125, U.S.A.

For information above B.M.U.G. contact the General Secretary, B.I.R., 32 Welbeck Street, London W1M 7PG.

A SYMPOSIUM ON RADIOISOTOPES IN CARDIOLOGY

Jointly organized by The British Institute of Radiology and the British Cardiac Society will be held on Wednesday, September 29, 1976, at the Greenwood Conference Centre, Guy's Hospital.

A review of the present position will be given by U.K. and overseas speakers. A limited time will be allocated to original presentation for which abstracts in not more than 200 words should be submitted by June 30.

Registration fee: £9·50 including lunch, morning coffee and afternoon tea.

Further details and registration forms will be available from The Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Attendance may be limited and registrations will be accepted in the order they are received.

8TH CONGRESS OF THE SOCIETY OF HUNGARIAN RADIOLOGISTS AND 12TH ANNUAL MEETING OF THE EUROPEAN SOCIETY FOR RADIATION BIOLOGY

To be held in Budapest, Hungary, October 19–22, 1976.

For further information please contact the Congress Office (H-1361 Budapest, PO Box 32, Hungary).

RADIATION PROTECTION: AN EXAMPLE OF ACTION AGAINST MODERN HAZARDS

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P. no. 33, 92260 Fontenay-aux-Roses, France.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

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Printed in Great Britain by Lund Humphries
London and Bradford
Published by The British Institute of Radiology
32 Welbeck Street, London W1M 7PG

ISSN 0005-1285
08406

.11.76

Volume 49 Number 582
June 1976

THE BRITISH JOURNAL OF RADIOLOGY

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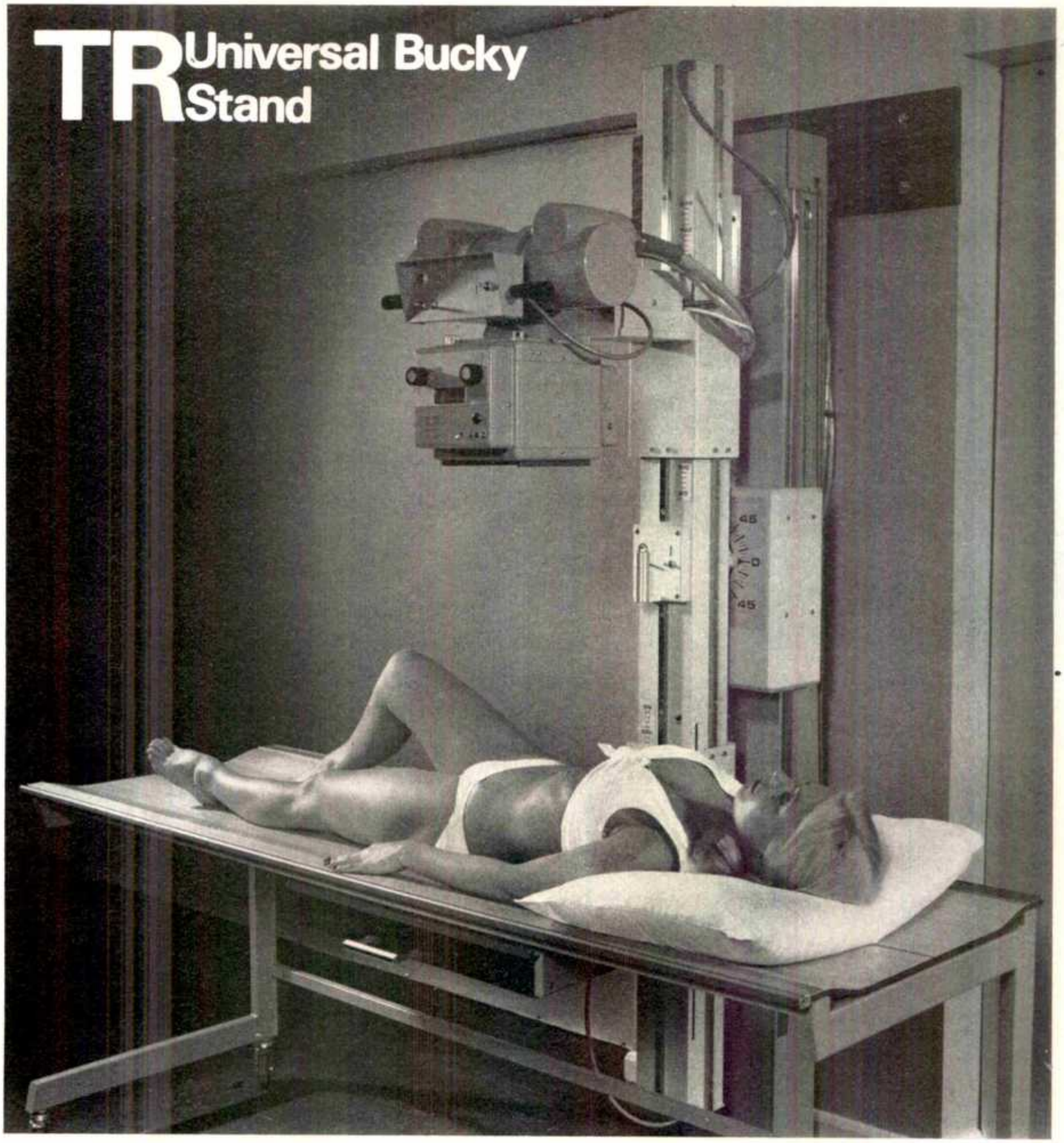

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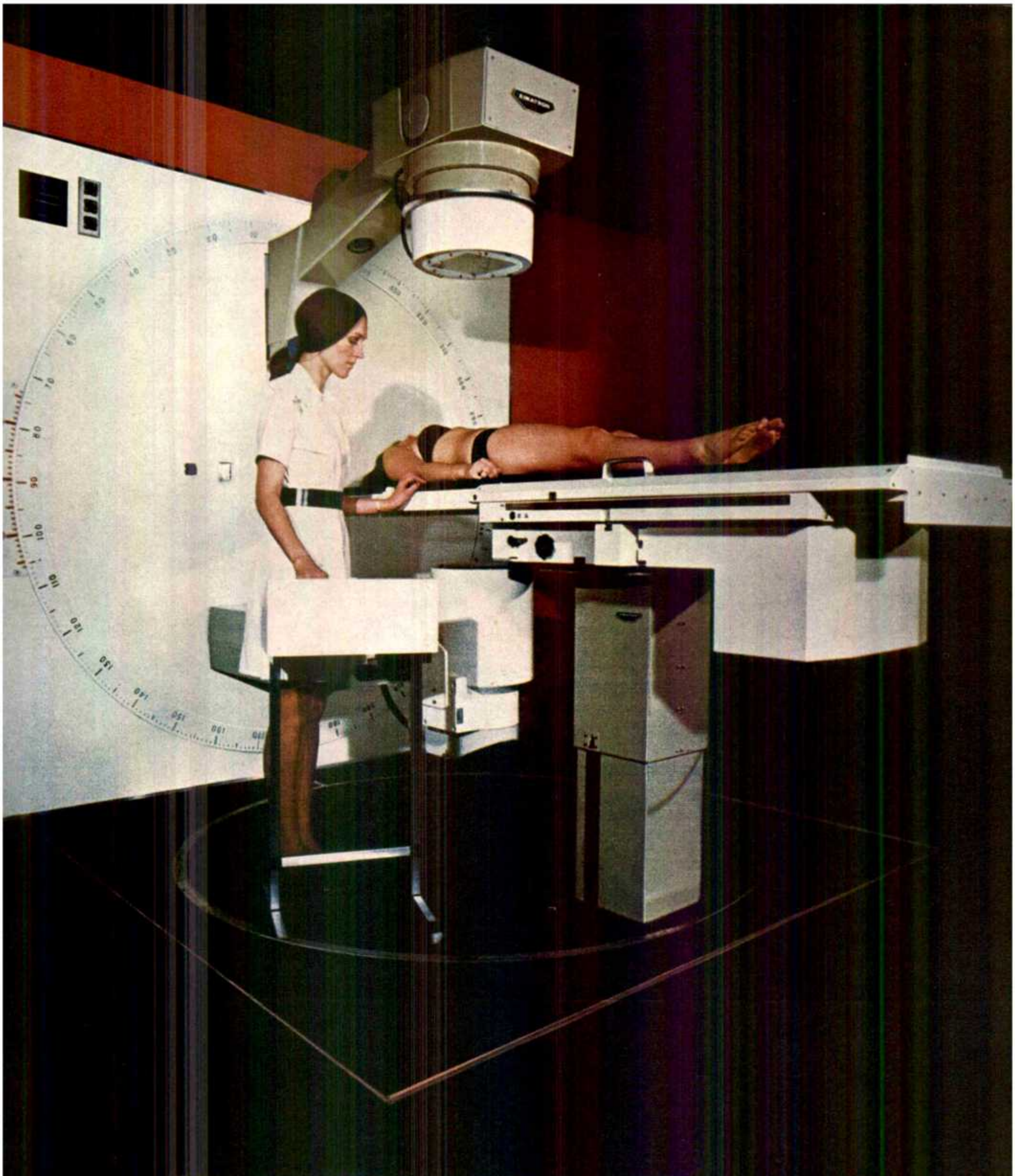
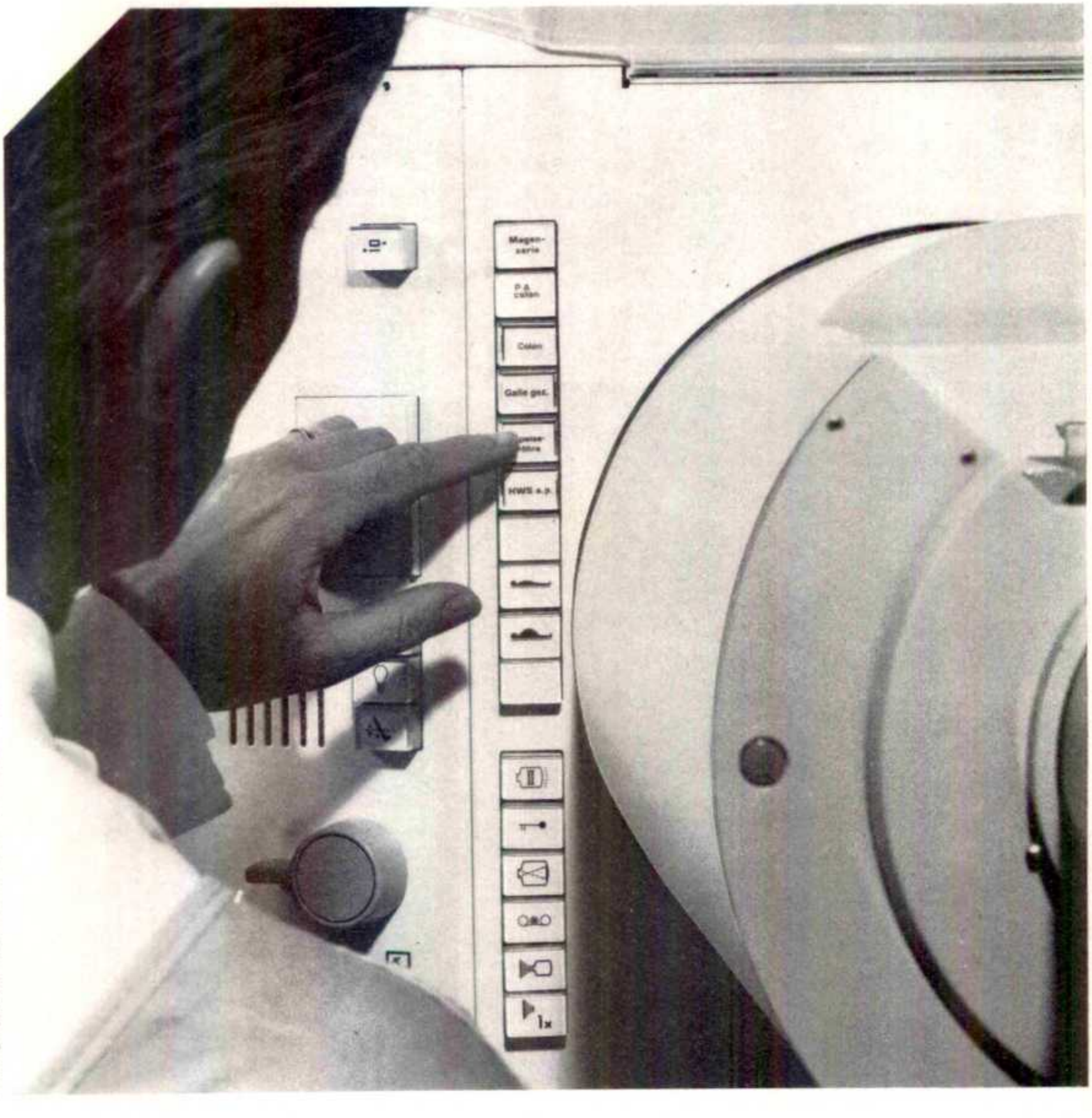


Ximatron Treatment Planning Simulator

TEM Instruments Limited

twick Road, Crawley, Sussex, RH10 2BG, England. [illegible]

The generator at your fingertips. Thanks to the modular principle.

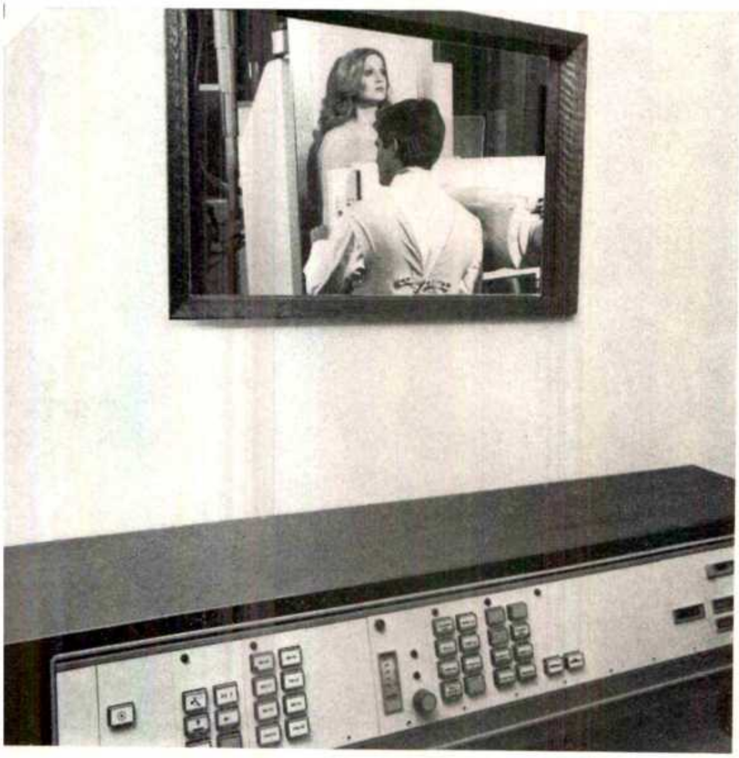


Photographs by courtesy of Rijnoord Hospital, Alphen a.d. Rijn, The Netherlands.

modular means made to measure

The Philips Modular Generator series gives you full control of your generator while attending to the patient being examined. Controls for the Modular Generator are integrated in the DIAGNOST 73, within your natural reach so that you can select the appropriate parameters for every routine examination yourself. This system of anatomically programmed radiography leaves you free to concentrate on the patient, while retaining full control over the generator.
The modular construction allows the installation to be designed to meet your specific requirements, and to be extended as your department grows.
Modular means made to measure.

1



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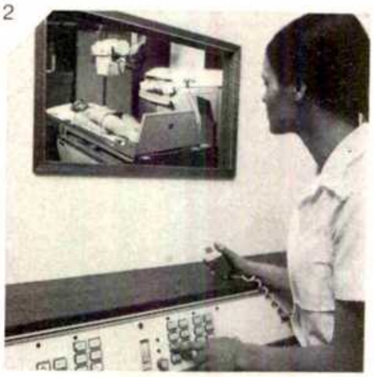

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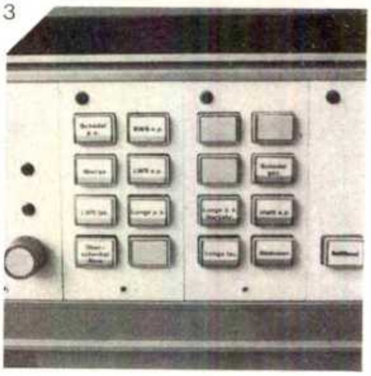


1. All controls are, of course, duplicated on the generator desk.

2. + 3. For bucky work on the DIAGNOST 73, or an additional unit, the generator desk incorporates additional controls for anatomically programmed radiography. You are free to distribute the settings you require over the available push-buttons in whatever way you like.

4. The generators incorporate automatic kV and mA control ensuring bright, evenly illuminated fluoroscopy pictures. If necessary, you can override the automatic settings for special fluoroscopic techniques.

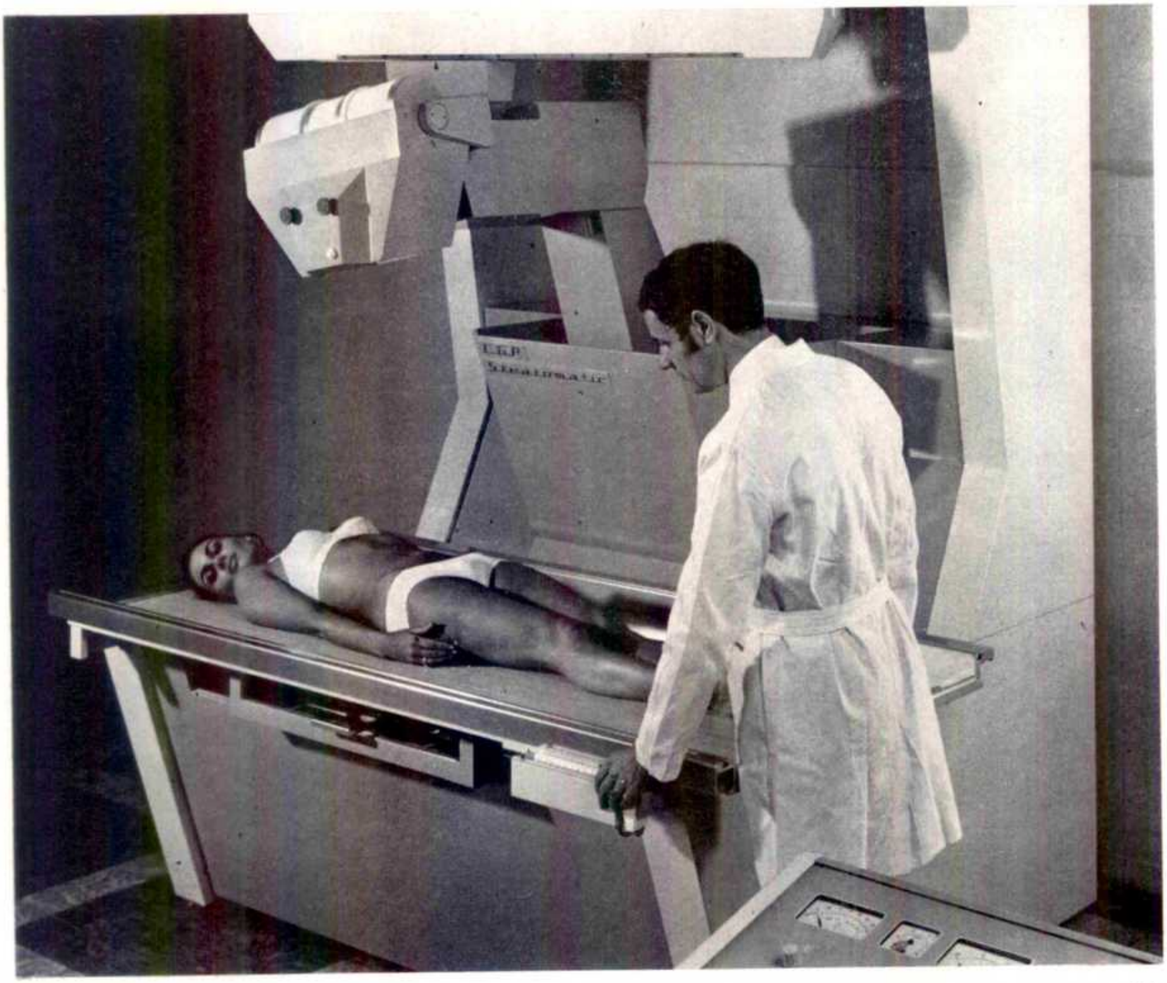
For further details contact Philips Medical Systems, Eindhoven, The Netherlands, or Philips Medical Systems Ltd., 45 Nightingale Lane, London SW12 8SX.

PHILIPS

PHILIPS

Medical Systems

A high precision unit providing electronically controlled tomography



STRATOMATIC

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CGR

A rigid free-standing high-precision tomographic unit, giving Zonography, multi-direction rectilinear, circular and tri-spiral movements.

Electronic speed regulation devices according to focus film distance provide constant photographic effect at all angles. For simplicity of use and quality of films obtained, the Stratomatic is unsurpassed.

Full details and specifications from
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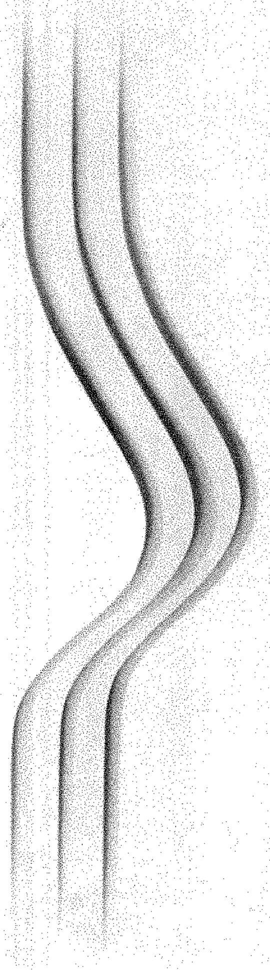
Astronaut House, Feltham, Middx. Tel: 01-890 8166

GEVAERT AGFA-GEVAERT

Mammography MR

The Agfa-Gevaert MR mammography system offers optimum results using the lowest radiation dose. The system is a combination of a special high sensitive film, Mamoray RP 3, with a rare earth intensifying screen, MR 50, specially created for mammography. The MR 50 screen is blue emitting and the Mamoray RP 3 film is blue sensitive. This means there is no need to change the darkroom lighting and, in addition, RP 3 is a rapid processing film which can be run through your processor together with other X-ray films.

AGFA-GEVAERT Ltd.,
Medical X-Ray Sales Dept.,
27, Great West Road,
Brentford, Middx., TW8 9AX.
Tel: 01-560 2131



- Minimal radiation dose.
- Outstanding definition.
- Optimum contrast.

What the hospital board should see if it wants the radiotherapy department to be more efficient.

Fast and efficient treatment does not start with the treatment unit.

In order to ensure maximum patient flow it is essential that the actual treatment machine is left free to function to full capacity and thus fulfil its proper role.

This involves introducing a localiser/simulator to the radiotherapy department.

Philips have developed a unit that will function with all megavoltage equipment, but of course it was designed to be fully compatible with the famous SL75 series of linear accelerators and the Cobalt 60 unit.

Simultaneous movements and variable speed control ensure rapid and accurate patient set-up. An exceptionally wide range of table top movements, combined with the great flexibility of the unit permit optimum localisation and simulation of any treatment routine.

The localiser/simulator's interactive design means it can be linked to select and confirm routines and data print-out.

The common design philosophy behind all the equipment in the Philips Integrated Therapy Programme assures that the hospital's long-term plans as well as immediate requirements are fulfilled.

The Programme includes contact therapy equipment, orthovoltage and Cobalt units, and high energy X-ray and electron accelerators.

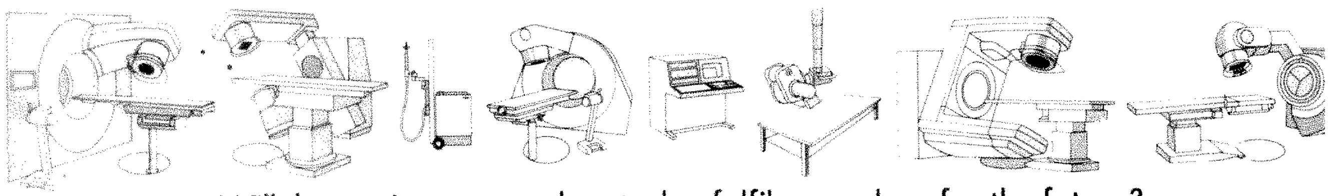
All this is complemented with ancillary equipment like a computerised treatment planning system.

In order that the radiotherapy staff can operate at maximum efficiency, it is important that they have the tools with which to achieve this with minimum stress.

The Philips localiser/simulator is just one example.

Why not find out more by writing to one of the addresses below?

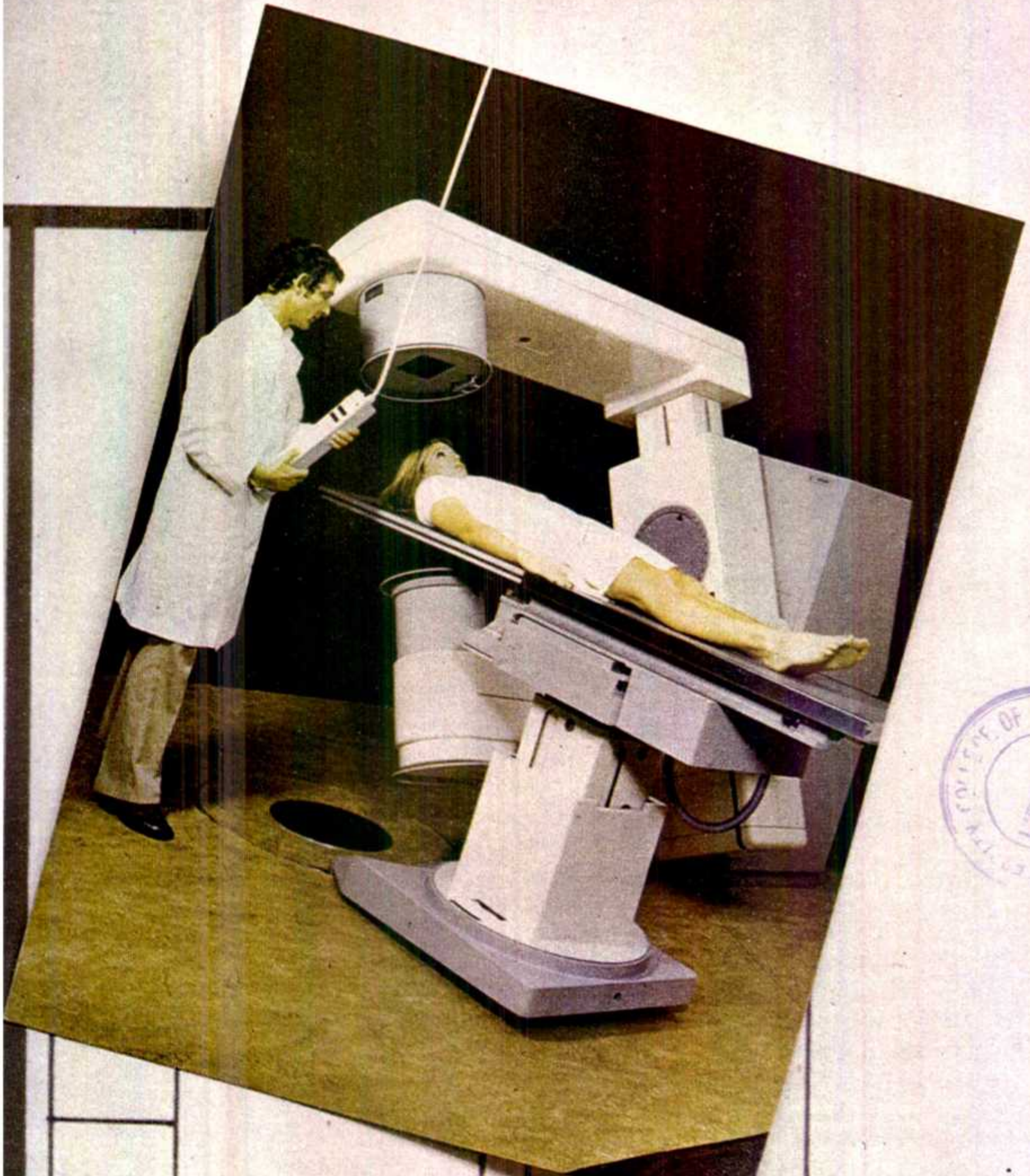
Then the hospital board can see just how important the Philips Integrated Therapy Programme is to the future of the radiotherapy department.



Will the equipment you buy today fulfil your plans for the future?
Philips Integrated Therapy Programme.

If you would like to know more about the Philips Integrated Therapy Programme, please write to: N.V. Philips, Medical Systems, Eindhoven, The Netherlands.

localiser/simulator



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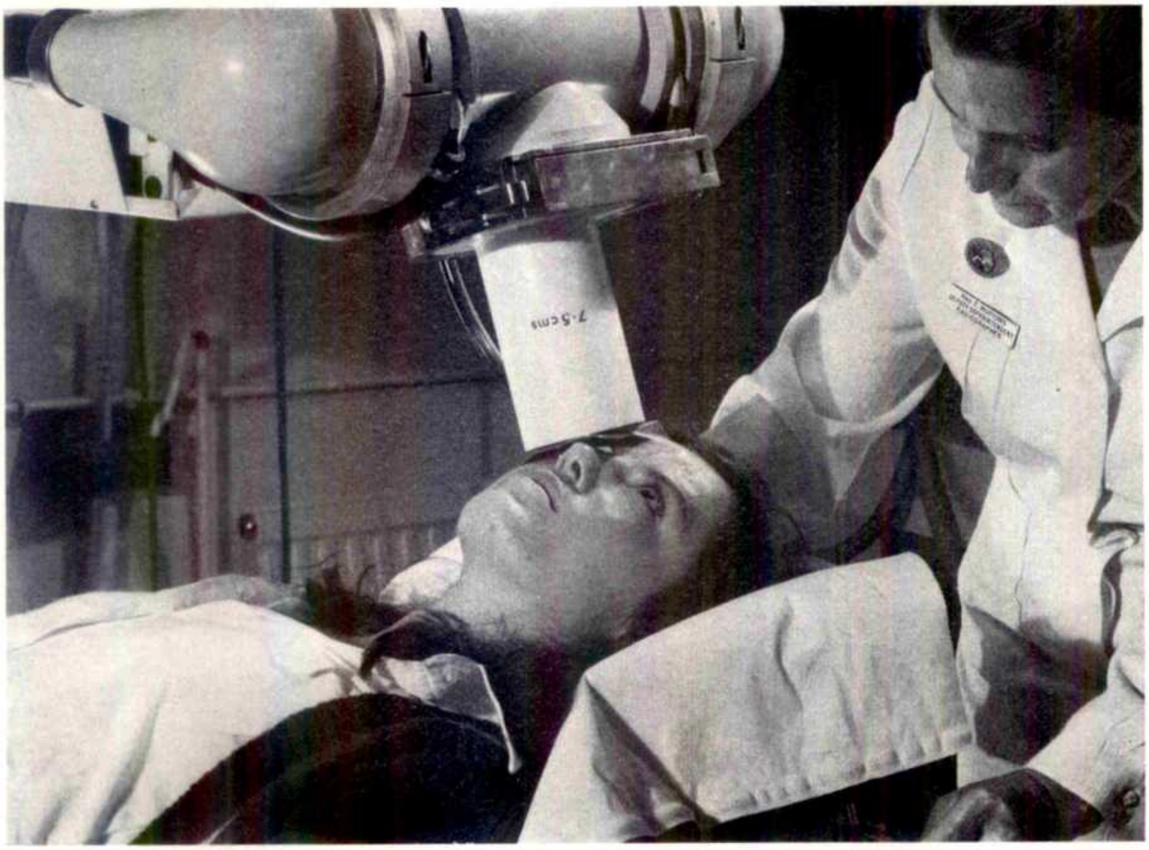
PHILIPS



Therapax 150 a new Superficial Radiotherapy Unit in the 50–150 Kv range

The Therapax Superficial Radiotherapy Unit has been specifically designed by Pantak to meet the new D.H.S.S. specification for UK Hospitals – RASMP/75 and provides a dependable, easily positioned source of X-radiation in the 50-150 Kv range.

Therapax is the most technologically advanced unit available at this energy level and is based on a widely used and fully proven X-ray generator. It provides pre-selected treatment programmes with main and back-up timers that ensure optimum patient protection.

Pantak, a British company within the EMI Group has over 30 years experience in X-ray systems and is in a position to provide comprehensive technical and back-up services.

EMI

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Any changed faces round your way lately?

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the face of
adiography with
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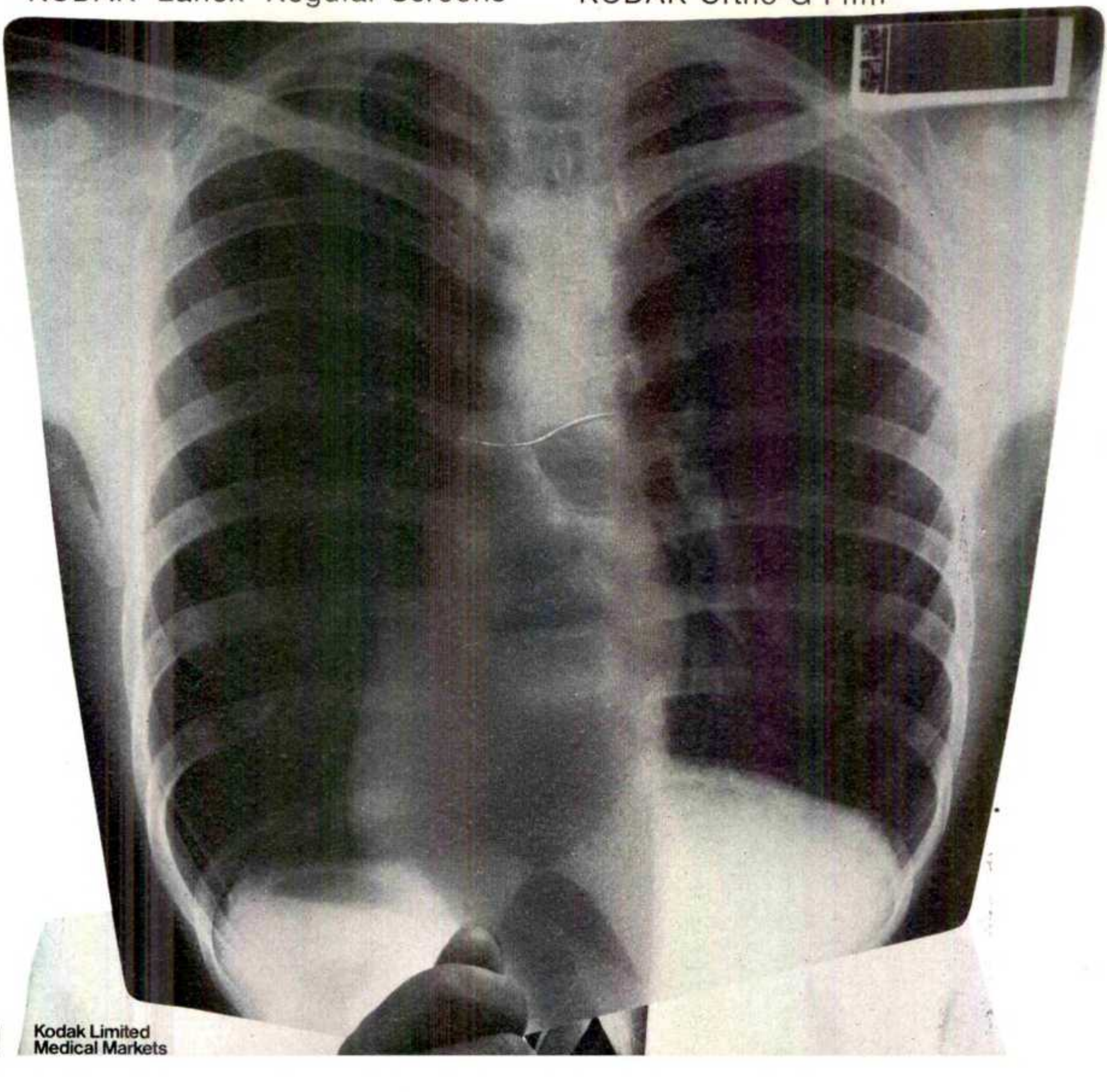
Here's a Radiologist who's been given high image quality. He knows the patient was given a low dosage, too. One thing he doesn't know. **The patient moved.** Because, as well as high image quality at low dosage levels, KODAK 'Lanex' Regular Screens and KODAK Ortho-G Film allow greatly reduced exposure times.

Talk to your Kodak Technical Sales Representative now, and change a few faces.

KODAK 'Lanex' Regular Screens KODAK Ortho-G Film



Kodak Limited
Medical Markets

The Urografin range of contrast media.

Each trade name provides a guide to the iodine concentration of the individual medium and allows easy calculation of dosage requirements.

Included in the range are two new presentations:

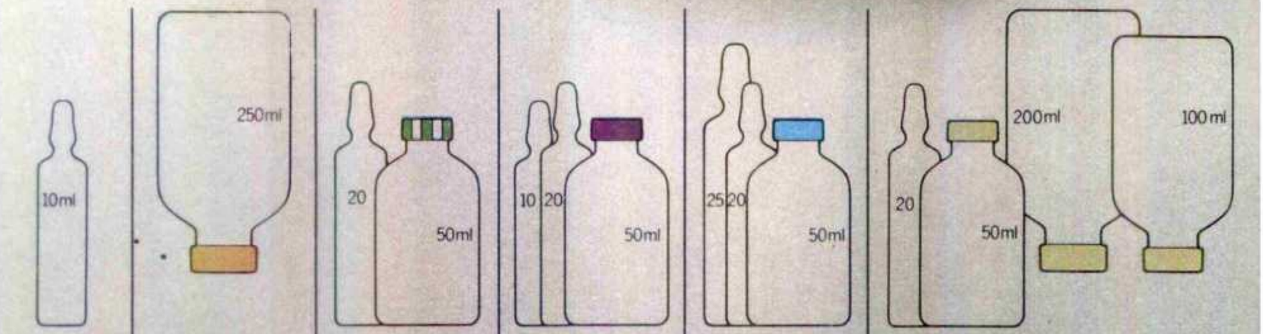
a 20ml ampoule of Urografin 310M, containing a 65% solution of meglumine diatrizoate, for use in peripheral arteriography and venography, and

a 20ml ampoule of Urografin 325 (58%) which will eventually replace the 25ml ampoule currently available.

Further information available on request.

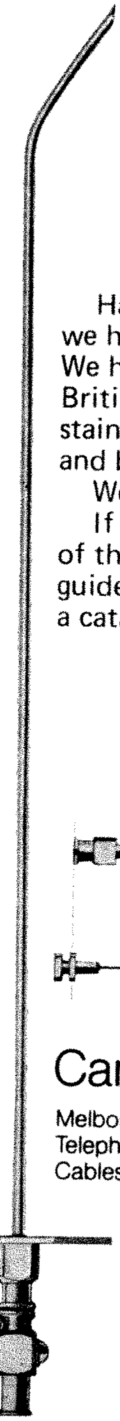
Schering Chemicals Ltd.,
Pharmaceutical Division,
Burgess Hill,
West Sussex RH15 9NE.

Schering



Urografin 150	Urografin 150 for infusion	Urografin 290	Urografin 310 M	Urografin 325	Urografin 370
formerly Urografin 30%	formerly Urografin 30% for infusion	formerly Urografin 60%	formerly Angiografin	formerly Urovison	formerly Urografin 76%

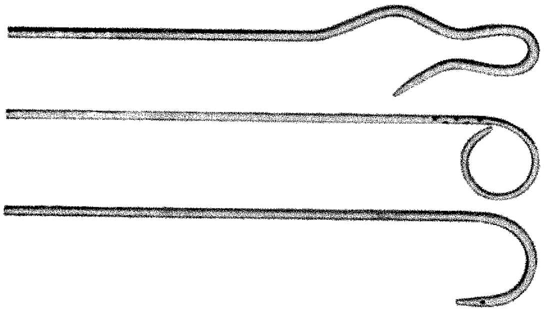
We'd like to make a further point about our new product line.



Last year, we introduced a new product line — a whole new range of catheters and guide wires — and very successful they are too.

We told you how the wires, British to their flexible core, are wound to exceptionally close tolerances. And how they feature a safety wire, a flexible tip, and optional Teflon coating.

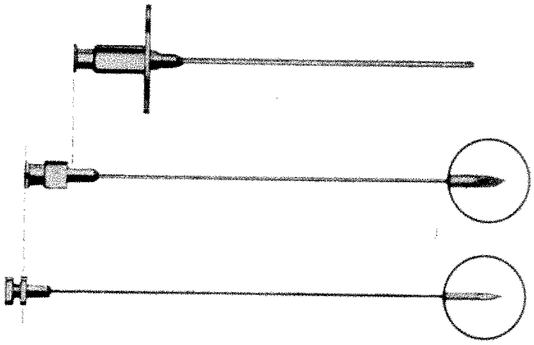
We told you, too, about our disposable catheters, available in radiopaque polythene or Teflon tubing. How, like the wires, they can be supplied ready heparinised. And how they are all sterilised with ethylene oxide, and sealed in airtight peel packs.



Having told you all that, we have just one more point to make. We have now introduced a range of British-made, high quality, stainless steel, re-useable percutaneous and biopsy needles.

We hope you will take our point.

If you would like further details of the Cambridge range of catheters, guide wires and needles, send for a catalogue today.



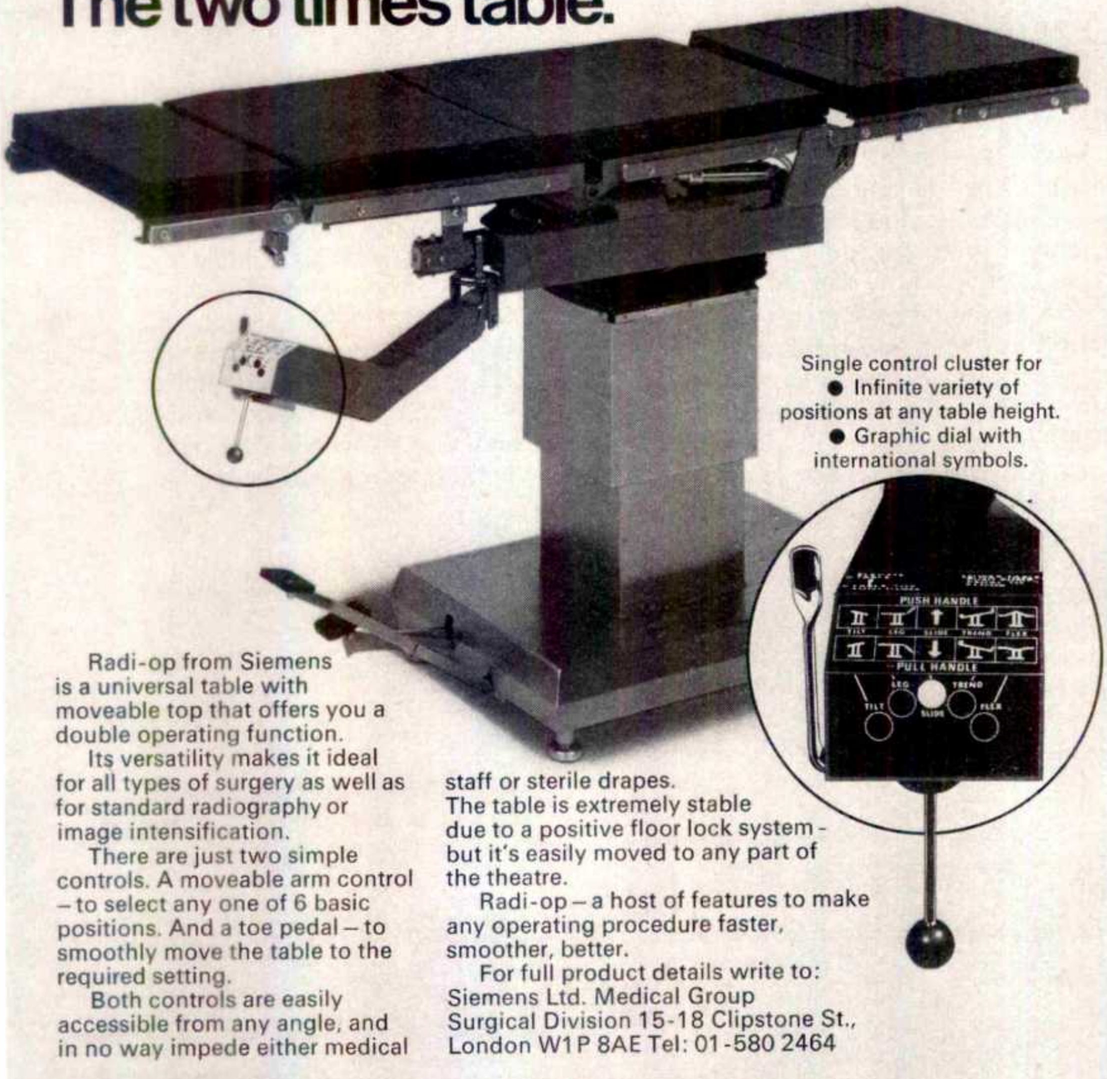
Cambridge Instruments

Melbourn, Royston, Herts SG8 6EJ
Telephone Royston (0763) 60611
Cables Metres Cambridge. Telex 81124

TIB 2/75

SIEMENS

The two times table.



Single control cluster for
- Infinite variety of positions at any table height.
- Graphic dial with international symbols.

Radi-op from Siemens is a universal table with moveable top that offers you a double operating function.

Its versatility makes it ideal for all types of surgery as well as for standard radiography or image intensification.

There are just two simple controls. A moveable arm control – to select any one of 6 basic positions. And a toe pedal – to smoothly move the table to the required setting.

Both controls are easily accessible from any angle, and in no way impede either medical staff or sterile drapes.

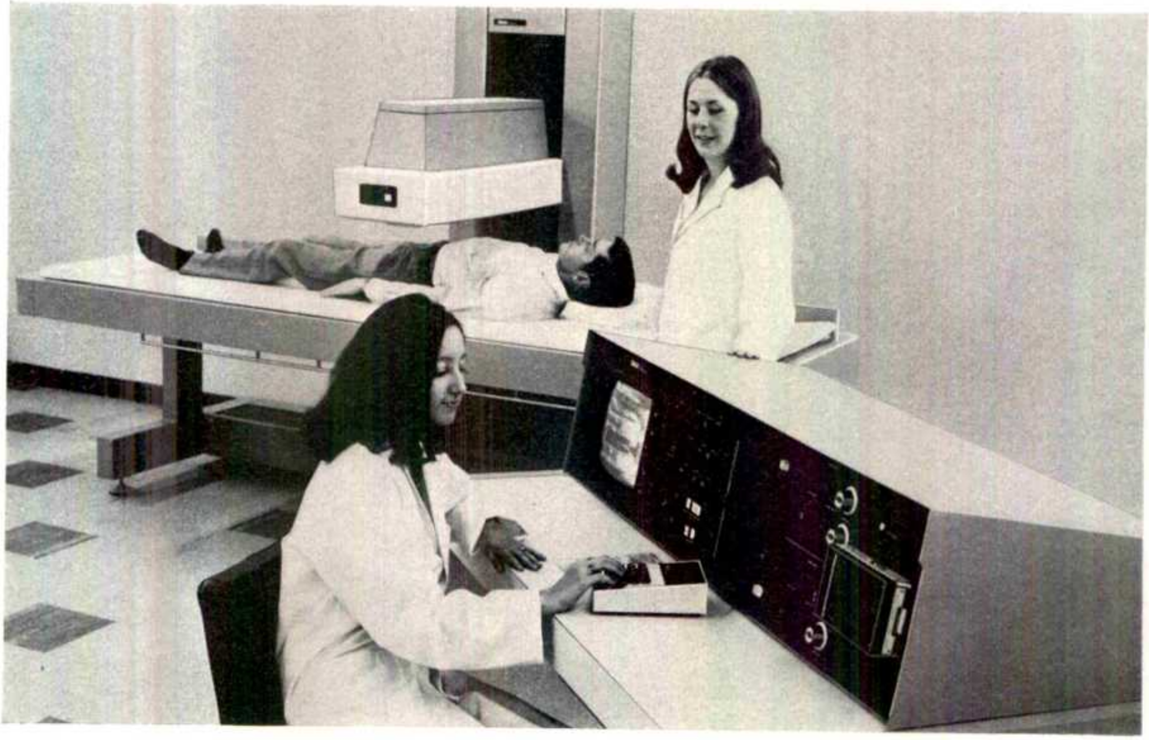
The table is extremely stable due to a positive floor lock system - but it's easily moved to any part of the theatre.

Radi-op – a host of features to make any operating procedure faster, smoother, better.

For full product details write to:
Siemens Ltd. Medical Group
Surgical Division 15-18 Clipstone St.,
London W1P 8AE Tel: 01-580 2464

For surgery, for radiography.
Radi-op from Siemens.

Improve your Image in 1976 with CLEON



The Cleon Imager, capable of both organ and whole body scanning, has been designed to meet the needs of the busy nuclear medicine department.

In "WHOLE BODY MODE" it has the ability to cope with a patient load three or four times faster than on a conventional rectilinear scanner, at the same time providing dual anterior and posterior skeletal images of such clarity and sharpness that the necessity to repeat small-area scans is virtually eliminated. When switched to "ORGAN-MODE", scans can be produced with speed comparable to (and in-depth resolution better than) a gamma camera.

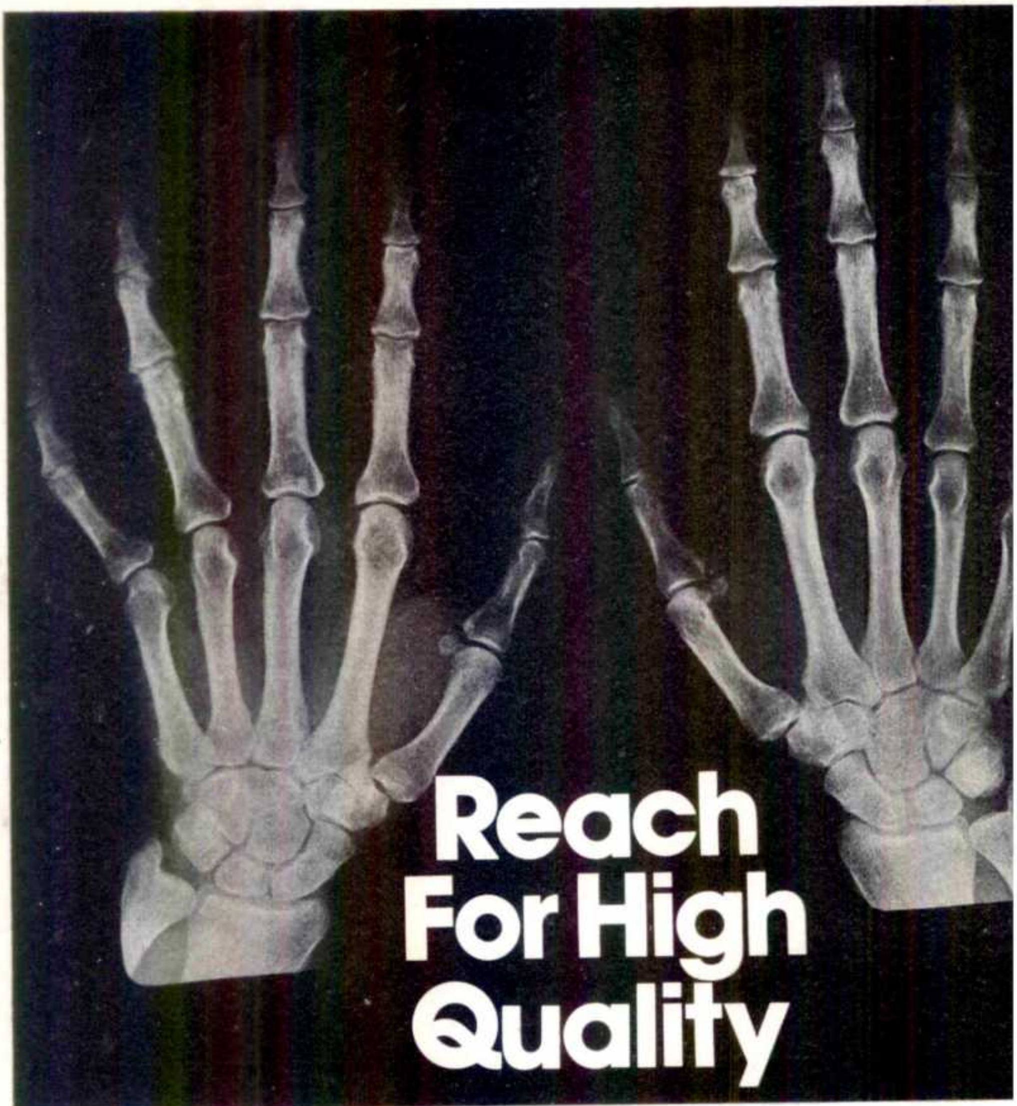
The Imager's display and recording options, enhancement of photo-images and the capability to playback stored data greatly increase its clinical usefulness. Reliability, rapidity of operation and high patient throughput mean increased utilisation and economy, along with improved diagnostic efficiency.

For further details, please contact Internuclear Ltd., the U.K. Distributors for Cleon equipment.

internuclear

Distributors for: Atomic Development Corp · Capintec Inc · Cleon Corp· Matrix Instruments · Medicor · NL Industries Inc.

INTERNUCLEAR LIMITED, 18 BATH ROAD, SWINDON, WILTS, SNI 4BA. Tel: 0793-30579



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'Polycon/Perfix' produces highly diagnostic radiographs in only 2½ minutes. Slight variations in development times produce the exact contrast required.

And 'Polycon' has plenty of life: it is usually replenished to a minimum of 200 per cent, but can be extended to 400 per cent!

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PA 3621

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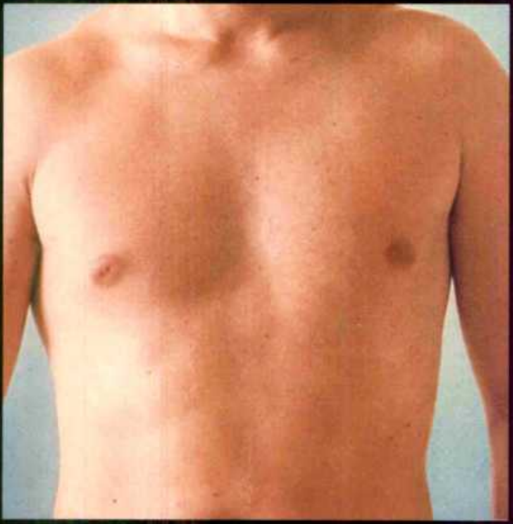

cassetteless chest system with automatic processing is a boon to any adiology department. In fact, Picker was the first to introduce this concep ack in 1968 with the Automatic Chestfilmer. This can handle over a third o our department's caseload in a single small room. But what about horizonta assetteless radiography? Picker leads here, too, with the Rapido® which tresses speed, efficiency, and superior diagnostic results for another third f your requirements. Don't settle for only half a cassetteless system. The ogical choice is Picker. For Picker has the experience where it counts – in e field and operating, with over 400 cassetteless systems installed or on rder throughout the world.

ull details from Mr. A. J. M. Spaapen, Picker International Operations GmbH 201 Auringen- Wiesbaden, Feldberg Strasse 6, West Germany.

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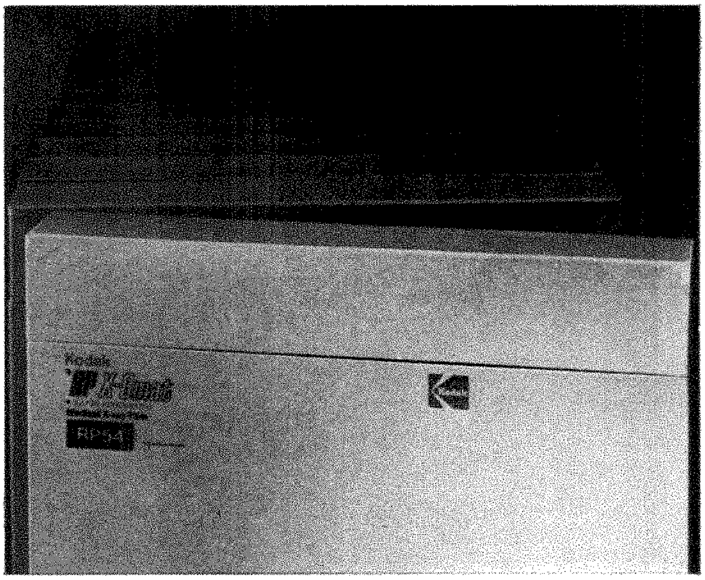

Parameters.

For Kodak, that's very much more than a buzz-word.

When it comes to producing 'Kodak' Film – like the range of twelve large-format X-ray films, there's a whole host of parameters by which the product is judged.

Altogether, from the time the raw materials enter the factory to the time the finished sheets of film are dispatched in their familiar boxes, no less than 1,000 different checks and tests are made against set parameters.

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They are exposed, and processed. They are subjected to sensitometric and physical monitoring tests.

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No less than 1,000 tests and checks. All because we try to satisfy the most important parameter of all. You.

Kodak: the people with the tradition of trust.

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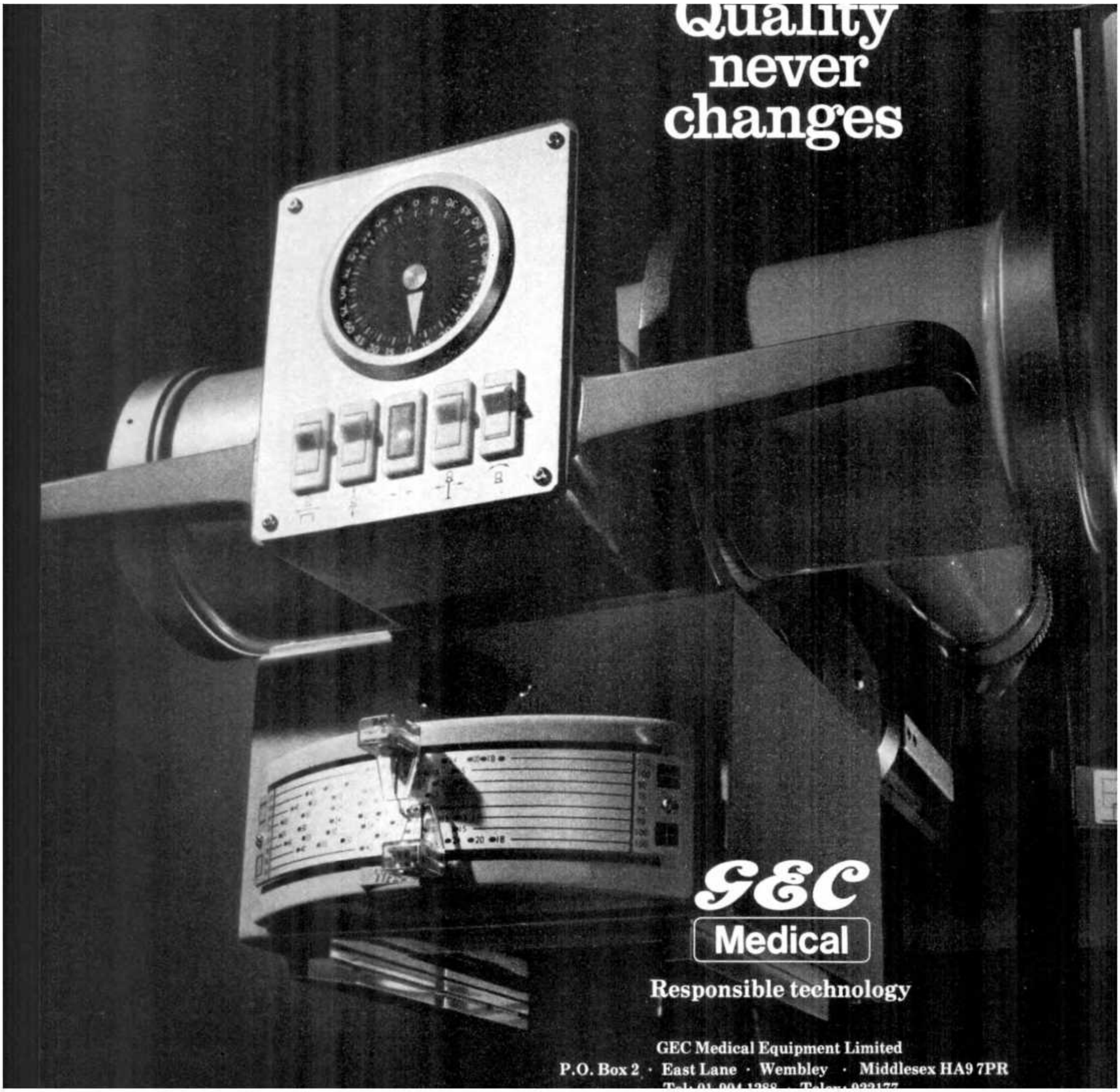

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Do you *use* or *choose* Guide Wires?

Are you the radiologist or the surgeon whose demands are so critical that only the very best will do - at any price?

Do you like variety, or have you found the one type which meets, exactly, all your needs?

Or are you the one whose responsibility it is to locate and purchase the right guide wires at the right price?

Whether you use or choose guide wires you really should take advantage of our offer to send you full details and free samples of our range.

We believe they are the very best available at any price .... but the funny thing is .... they are not the most expensive. In fact, you could find the better product you have been wanting costs no more, probably less, than the one you're currently using or choosing.

Simply call or write to our General Manager, Don Allen, and mention this advertisement. He'll do the rest. We're confident you won't regret it.

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COURSE IN PRACTICAL ECHOCARDIOGRAPHY

Department of Cardiology
Newcastle General Hospital
Westgate Road
Newcastle upon Tyne, NE4 6BE

12th–20th September 1976

This residential course is intended for physicians or senior technical staff interested in the use of diagnostic ultrasound in heart disease. Lectures will be given on the basic physics of ultrasound, the diagnostic uses of echocardiography in valvular heart disease, ischaemic heart disease, congenital heart disease and the most recent advances in cardiac ultrasonics. The emphasis of the course will, however, be on practical echocardiography. There will be individual tuition in the clinical use of ultrasound with ample opportunity for participants to perform examinations on all of the common cardiac defects, congenital or acquired.

The course fee is £30·00 and residential accommodation with full board can be provided, if required, in a University Hall of Residence. A limited number of places are available and applications should be made to Dr. Stewart Hunter, Department of Cardiology, Newcastle General Hospital, by 1st July 1976 at the latest.

UNIVERSITY OF QUEENSLAND

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The University invites applications for the following Foundation Chair:

CHAIR OF RADIOLOGY

within the newly created Department of Radiology. The applicant should have medical and specialist qualifications registrable in Queensland, a distinguished research record and experience in teaching and administration.

Closing date for applications *30 June 1976*.

Salary: The salary for a clinical Professor is £A29,955 per annum.

The University provides prescribed travelling and removal expenses, superannuation, study leave and housing assistance.

Additional information and application forms are obtainable from the Association of Commonwealth Universities (Appts.), 36 Gordon Square, London WC1H 0PF.

Queensland – Australia

Diagnostic Radiologist

required to work with partnership in Tropical city twenty miles to Barrier Reef.

Must be experienced in special procedures.

Single fares now – Return air fares after 12 months.

Partnership opportunity available.

Accommodation and Car provided.

Salary 20,000 pounds Sterling approx.

Partner available for interview in London in July.

Reply. Box No. 2 British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Postgraduate Course on Tumour Radiology

The Department of Radiodiagnosis of the University of Bristol will hold a postgraduate course on "Tumour Radiology: Relevance of Radiology to Clinical Management" on 15th and 16th July at the University Union, Bristol.

The theme will be the role of radiology in the diagnosis, treatment and clinical management of various tumours, and the subjects to be covered will include the reticuloses, cerebral tumours (including computerised tomography), bone tumours (including angiography and correlation of radiology and pathology), tumours of upper urinary tract, intrathoracic tumours in childhood and pancreatic tumours.

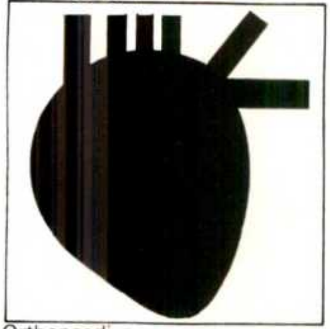
The speakers will be members of the University of Bristol Department of Radiology and the staffs of United Bristol Hospitals, Royal National Orthopaedic Hospital, London, Northwick Park Hospital, London, and St James's Hospital, Leeds.

Application forms from Miss D. Taylor, Department of Radiodiagnosis, Medical School, University Walk, Bristol BS8 1TD, to be returned by 29th June, 1976. Accommodation is available.

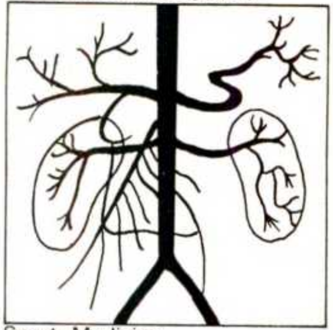
What do you expect
from a generator ?

FLEXIBILITY–EASE OF CONTROL–VERSATILITY OF APPLICATION–OUTPUT

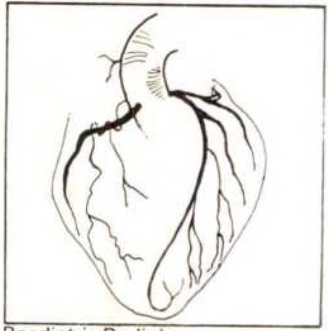
Cardangiography.



General Cine Angiography.



Coronary Angiography.



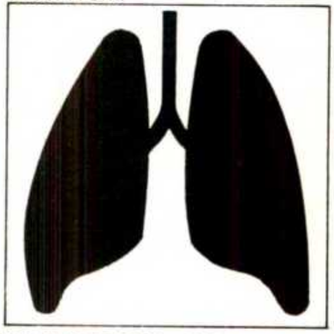
Orthopaedics.

Sports Medicine.

Paediatric Radiology.

Radiological Research.

Chest Work.



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Offers the following outstanding features

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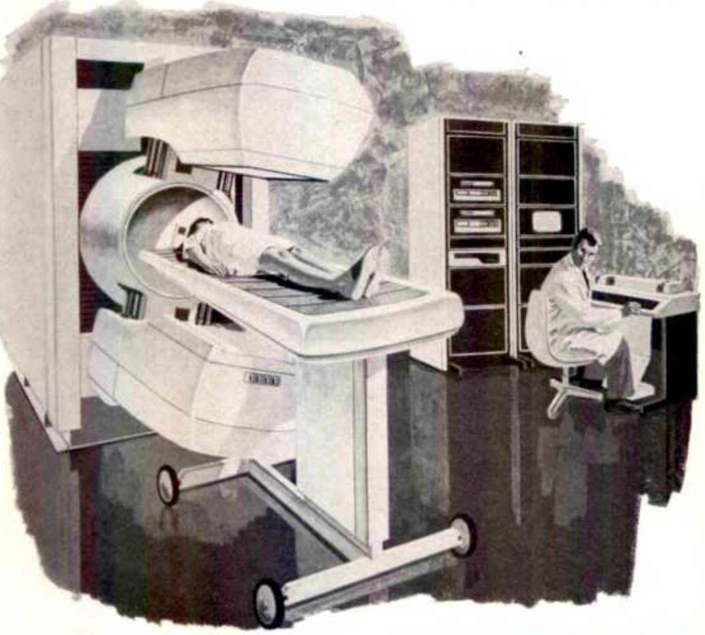
15/18 Clipstone Street, London W1P 8AE, 01-580-2464
Branches in *Aberdeen, Birmingham, Bristol, Bury St. Edmunds, Edinburgh, Glasgow, Leeds, Liverpool, Manchester, Newcastle and Reading.*
Agents in *Belfast and Newport.*

A NEW POSITRON CAMERA SYSTEM FEATURING BOTH MULTI-PLANE TOMOGRAPHIC IMAGING AND TRANSVERSE AXIAL TOMOGRAPHY...

With Count Rate Capability in Excess of 10^7 Counts Per Second Per Head.



Based on a prototype developed at Massachusetts General Hospital, this new System manufactured by The Cyclotron Corporation is ideally suited to rapid dynamic studies. In multiplane tomographic imaging, the sensitivity of this advanced System is one to two orders of magnitude greater than that of other systems. In the transverse axial mode ten independent sections are made simultaneously.

Data acquisition and processing are controlled by a dedicated computer which is supplied as part of the System. Display is fully quantitative with selectable regions of interest. Images are corrected for attenuation and detector non-uniformity. The System includes software and provision for Fortran programming by the user.

The Cyclotron Corporation is well-known for its compact cyclotron systems which are ideal for production of short lived positron emitting isotopes ^{11}C ^{13}N ^{15}O and ^{18}F plus other isotopes used in nuclear medicine. Generator produced nuclides such as ^{68}Ga and ^{82}Rb also are positron emitters and may be used with the System.

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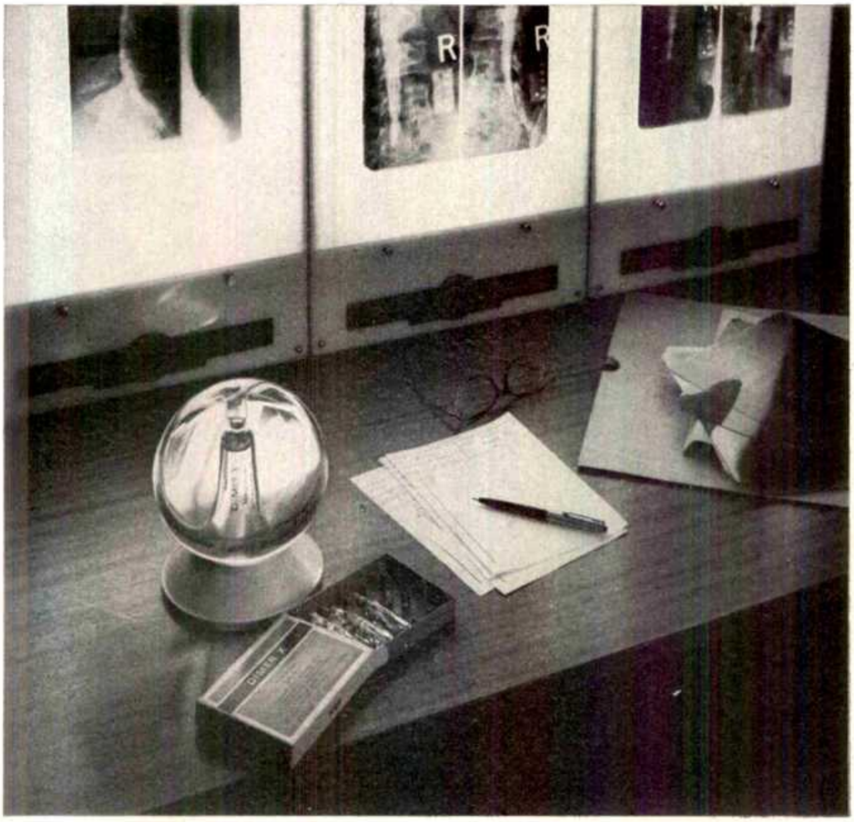
In the radiological assessment of low back pain and sciatica



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Excellent bone detail.

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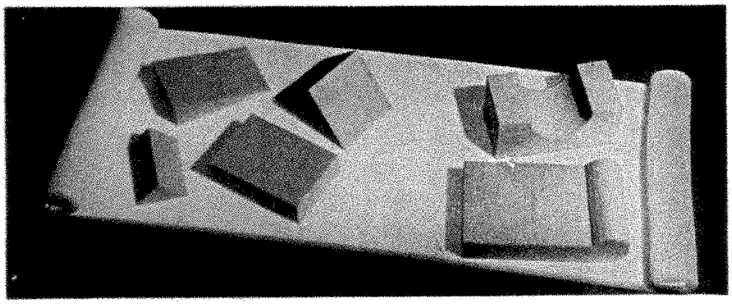

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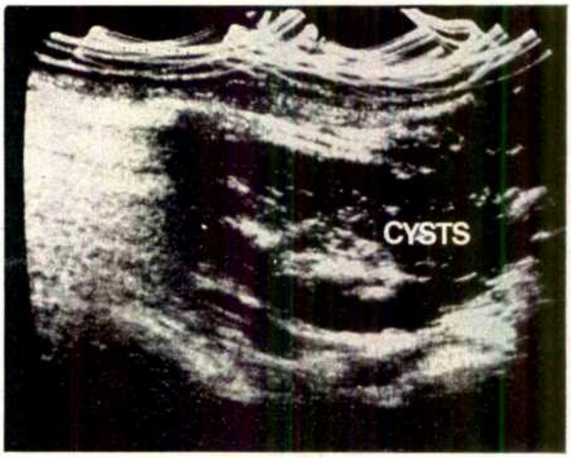

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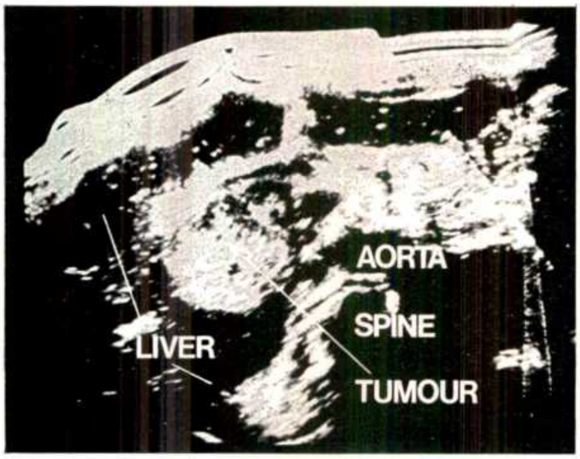

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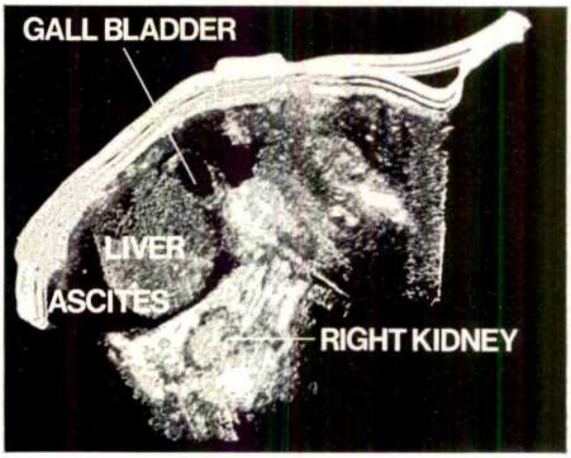

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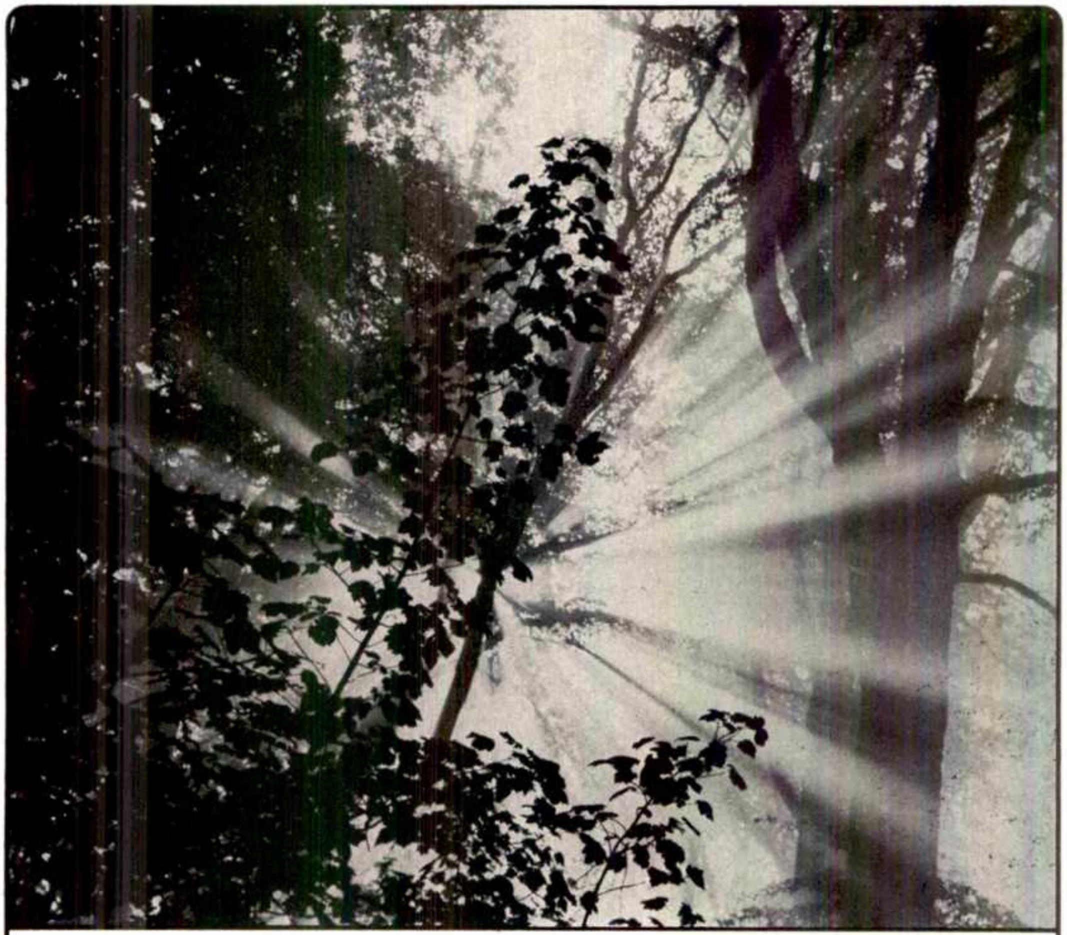

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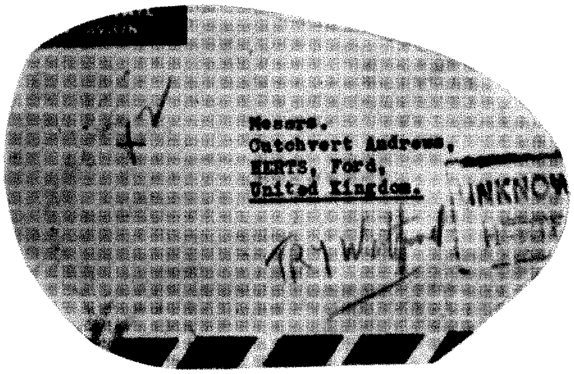
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1976, *British Journal of Radiology*, *49*, 481–482
VOLUME 49 NUMBER 582 JUNE 1976

The British Journal of Radiology

Radiology now

Contrast media for coronary and renal angiography*

There has been no major change in arteriographic media for more than 15 years. The use of dimers, non-ionic media and finely emulsified oils for angiography may be on the horizon, but for the next few years the sodium and meglumine salts of the tri-iodobenzoates will be the only media in routine use. There is wide agreement on the type and dose of contrast medium for studies of the arteries to the heart and brain but this is not so for the kidney.

There is no clear evidence that any one of the anions (diatrizoate, iothalamate or metrizoate) are superior to any other, but the choice of cation for cerebral and coronary angiography can be crucial. The best medium for carotid angiography is a pure, or nearly pure meglumine compound. Pure meglumine salts are, however, a poor choice for coronary arteriography since there is a high incidence of ventricular fibrillation (Snyder *et al.*, 1971). Their use had been prompted by the known high risk of ventricular fibrillation with the concentrated pure sodium salts (Gensini and Di Giorgi, 1964). It has now been shown that the closer the sodium concentration of the medium is to that of plasma, the less the ECG abnormalities and the lower the incidence of ventricular fibrillation (Paulin and Adams, 1971). The media in almost universal use are those that contain 370 mg of iodine/ml., with 15 per cent of the contrast medium as a sodium salt, the remaining major cation being meglumine.

Renal arteriography is accepted as a reasonably safe procedure. There are several transient effects on renal blood flow and function, but no long-term effects in the vast majority of patients. Renal angiography is normally followed by a transient fall in glomerular filtration rate (Bunnell and Greene, 1965), a transient reduction in renal extraction of para-amino hippuric acid (Danford *et al.*, 1969; Sorby and Hoy, 1968), and a biphasic change in renal blood flow: an initial increase followed by a longer fall, with rapid return to normal (Russell and Sherwood, 1974; Sherwood and Lavender, 1969; Caldicott *et al.*, 1970).

The choice of cation for renal angiography seems unimportant, the present evidence pointing to only marginal and probably insignificant differences between sodium and meglumine salts. Iodine concentration and total volume injected are the important variables. Solutions with 280–310 mg of iodine per ml. are commonly recommended in text-books and by most manufacturers, but in a recent survey by questionnaire, over half of a sample of 96 angiographers from the United States of America and Europe use media with iodine concentrations of 370 mg/ml. or more for selective renal angiography (Talner and Saltzstein, 1975). They do so because they believe that they obtain more information from the angiogram, without an appreciable increase in risk.

Only a few investigators have compared the effects of media of differing iodine concentrations. Hollenberg *et al.* (1968) and Metys *et al.* (1971) included agents with concentrations of 280 as well as 370 mg of iodine per ml. in their studies on the renal effects of aortography in man. They showed no lasting harmful effect. Talner and Saltzstein (1975) compared the effects of Renografin 76 per cent (iodine concentration 370 mg/ml.) and Renografin 60 per cent (iodine concentration 290 mg/ml.)† for selective renal arteriography in the dog. At doses of 0·3 ml. per kg. they could show no significant difference for the two media in the renal extraction of para-amino hippuric acid (believed to be one of the most useful and sensitive indicators of renal damage due to contrast agents), or in the levels of lactic dehydrogenase in the urine. No abnormal histological changes could be identified. The case for the judicious use of media with iodine concentrations of 370 mg/ml. in problem patients with normal renal function is strengthened by this study.

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*Reprints from: Dr. P. Armstrong, Department of Radiology, King's College Hospital, Denmark Hill, London, S.E.5.

†Renografin is a mixture of meglumine and sodium diatrizoate, the meglumine/sodium ratio being 66:10. These agents are marketed under the trade name of Urografin in Great Britain (Schering).

But what about the patient in renal failure? The available evidence suggests that renal arteriography on these patients does not result in worsening of the renal failure (Mena *et al.*, 1973; Metys *et al.*, 1971; Walsh *et al.*, 1970), provided care is taken not to inject whilst the catheter is obstructing the renal artery. This risk is greater than in the normal population, since the renal artery is often small in these patients. Mena *et al.* performed selective renal arteriography with Renografin 76 per cent† on 143 patients with acute or chronic renal parenchymal disease, adapting the dose to take account of any reduction in renal mass due to disease. The procedure did not aggravate the underlying renal failure in any of these patients.

Acute renal failure directly due to renal arteriography is rare, but a very small number of patients do develop this complication even though the procedure has been technically satisfactory and standard doses of contrast medium have been used. The incidence at the Mayo Clinic was eight patients out of 7,800 undergoing abdominal or thoracic angiography (Port *et al.*, 1974). Five out of the eight had conditions leading to underperfusion of the kidneys such as congestive cardiac failure, bilateral renal artery stenosis and arteriovenous fistula, but there is no really satisfactory explanation why a tiny proportion of patients should develop such a serious response. It does not appear to be related to the type or concentration of the contrast medium chosen for the procedure.

The choice of contrast media for angiography is often a compromise between diagnostic information and harmful effects. The studies quoted suggest that media with iodine concentrations of 370 mg/ml. do no more harm in the kidney than the less concentrated media at present in widespread use. In some patients the less concentrated agents may produce perfectly satisfactory angiograms, particularly where high-powered generators permit optimum exposure factors, but for others the use of the more concentrated solutions seems justified.

P. Armstrong.

REFERENCES

Bunnell, I. L., and Greene, D. G., 1965. Rewards and hazards of selective renal arteriography. *Journal of the American Medical Association*, *194*, 1177–1180.

Caldicott, N. J. H., Hollenberg, N. K., and Abrams, H. L., 1970. Characteristics of response of renal vascular bed to contrast media. *Investigative Radiology*, *5*, 539–547.

Danford, R. O., Talner, L. B., and Davidson, A. J., 1969. Effect of graded osmolalities of saline solution and contrast media on renal extraction of PAH in the dog. *Investigative Radiology*, *4*, 301–305.

Gensini, C. G., and Di Giorgi, S., 1964. Myocardial toxicity of contrast agents used in angiography. *Radiology*, *82*, 24–34.

Hollenberg, N. K., Rosen, S. M., O'Connor, J. F., Potchen, E. J., Basch, R., Dealy, J. B., and Merrill, J. P., 1968. Effect of aortography on renal haemodynamics in normal man. *Investigative Radiology*, *3*, 92–95.

Mena, E., Bookstein, J. J., and Gikas, P. W., 1973. Angiographic diagnosis of renal parenchymal disease. *Radiology*, *108*, 523–532.

Metys, R., Hornych, A., Burianova, B., and Jurka, J., 1971. Influence of tri-iodinated contrast media on renal function. *Nephron*, *8*, 559–565.

Paulin, S., and Adams, D. F., 1971. Increased ventricular fibrillation during coronary arteriography with a new contrast medium preparation. *Radiology*, *101*, 45–50.

Port, F. K., Wagoner, M. D., and Fulton, R. E., 1974. Acute renal failure after angiography. *American Journal of Roentgenology*, *121*, 544–550.

Russell, S. B., and Sherwood, T., 1974. Monomer/dimer contrast media in the renal circulation: experimental angiography. *British Journal of Radiology*, *47*, 268–271.

Sherwood, T., and Lavender, J. P., 1969. Does renal blood flow rise or fall in response to diatrizoate. *Investigative Radiology*, *4*, 327–328.

Snyder, G. F., Formanek, A., Frech, R. S., and Amplatz, K., 1971. The role of sodium in promoting ventricular arhythmia during selective coronary arteriography. *American Journal of Roentgenology*, *113*, 567–571.

Sorby, W. A., and Hoy, R. J., 1968. Renal arteriography and renal function. The short term effect of aortography, selective renal arteriography, adrenalin suppression and renal venography on PAH extraction ratio. *Australasian Radiology*, *12*, 252–255.

Talner, L. B., and Saltzstein, S., 1975. Renal arteriography—the choice of contrast material. *Investigative Radiology*, *10*, 91–99.

Walsh, P. C., Gittes, R. F., and Lecky, J. W., 1970. Aortography in experimental renal failure. *Radiology*, *97*, 33–37.

1976, *British Journal of Radiology*, *49*, 483–501

Computerized tomography and angiography in subarachnoid haemorrhage

By B. E. Kendall, F.R.C.P., F.R.C.R., B. C. P. Lee, M.R.C.P., F.R.C.R. and E. Claveria, L.M.S.

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(*Received January, 1976*)

ABSTRACT

Our study of 100 multiple aneurysm cases show that 66 survived the initial danger period either with surgery, or by conservative treatment. Of these only one may have died subsequently from bleeding from an incidental aneurysm, during a continuing follow-up period now averaging more than seven years. In a separate series of 75 patients presenting clinically with subarachnoid haemorrhage it was possible to lateralize or approximately localize the site of bleeding by CAT in 56; 31 were from aneurysms and 13 from arteriovenous malformations. In the remaining 19 cases CAT was unhelpful in indicating the site of haemorrhage; 12 had aneurysms; no cause was found in the remainder. CAT was more valuable in localization in the seven days following the haemorrhage (86 per cent) than later (34 per cent).

The low risk of bleeding from incidental aneurysms makes us feel that treatment confined to the lesion which is responsible for the subarachnoid haemorrhage is not an unreasonable policy in the large majority of these patients. Detailed angiographic study of the site of haemorrhage is performed, but once this has been achieved, more extensive angiography is not routine, but is determined by the requirements of the surgery directed at the site of haemorrhage.

The poor prognosis of patients who have been treated conservatively after a recent bleed from an intracranial aneurysm makes consideration of surgical treatment an urgent matter (Pool and Potts, 1965). The practicability of the various possible surgical procedures is dependent firstly, on the accurate location of the bleeding site, and secondly, on detailed angiographic study of this region to show the anatomy of the lesion and of the adjacent arteries.

Location of the region of a haemorrhage is possible clinically in only a small proportion of cases (Locksley, 1969) and plain X rays of the skull, γ encephalography and electro-encephalography are only occasionally helpful. Angiography has been the most reliable means of establishing the site of haemorrhage as well as showing the detailed anatomy (Perrett and Bull, 1959) and frequently, therefore, it was the first study and was only supplemented by other investigations when there was still doubt as to which of multiple lesions had bled.

Actual leakage of angiographic contrast agents, showing that bleeding is taking place during angiography, has a poor prognosis and is fortunately rare (Jamieson, 1954; Goldstein, 1967; Hoff and Potts, 1969; Waga *et al.*, 1973). Local displacement of vessels due to haematoma or a more diffuse shift due to oedema or infarction are generally reliable in localizing the site of bleeding, but in most cases the aneurysms themselves and arterial spasm are the only abnormal findings. Large size, multiloculation and irregularity of the filled lumen are more common in aneurysms which have bled (Kricheff *et al.*, 1964; Wood, 1964; Du Boulay, 1965; Heiskanen, 1965). Arterial spasm tends to be most marked near the site of haemorrhage, though it may be present at some distance from it (Pool *et al.*, 1958; Fletcher, *et al.*, 1959; Du Boulay, 1963; Allcock and Drake, 1965; Pool and Potts, 1965; Brawley *et al.*, 1968; Katsiotis and Taptas, 1968; Griffith *et al.*, 1972; Symon *et al.*, 1973; Marshall, 1973). When aneurysms are multiple, some of these features are relative and can be best evaluated when the whole cerebro-vascular tree has been demonstrated (Kricheff *et al.*, 1964), and for this reason total cerebral angiography is used in many centres, unless there is clinical contra-indication. The increased safety of contrast media and modern angiographic techniques make the procedure technically simple with small risk of significant morbidity, in the region of 1 per cent in experienced hands (Heinz, 1973). Nevertheless, it is not entirely innocuous and is also expensive in terms of materials and skilled personnel time. It is, therefore, desirable to limit angiography to that which is of practical value in the patient's management.

Once the aneurysm responsible for recent bleeding has been definitely identified and shown to be suitable for direct surgery, the presence of other aneurysms is only strictly relevant to immediate surgical treatment when modification of the surgical approach allows them to be dealt with through the same craniotomy. If indirect surgery such as anterior cerebral clipping or carotid ligation is being considered, the presence of incidental aneurysms as well as the anatomy of the circle of Willis and the location of any stenosis of major cerebral vessels may be important and then three or four-vessel study may be necessary for immediate management. Up to the present time our clinicians have not considered it reasonable to subject more than a very few incidental aneurysms to the risk of separate elective surgery, nor do they suggest modification of the patient's life style because such aneurysms are known to be present. This policy is based on work suggesting that bleeding from incidental aneurysms is unusual (McKissock *et al.*, 1964) and that the morbidity of surgery on such lesions cannot, therefore, be justified. However, Heiskanen and Marttila (1970) reported a series of 84 patients with multiple aneurysms of which 76 survived the initial bleed. Ten of these patients suffered a further haemorrhage from which three died, in a follow-up period varying between 11 months and seven years. Eight of these bleeds were from previously unruptured aneurysms, five of which had been shown at the time of the previous angiograms, two had appeared on carotid trees which had previously been shown to be normal, while the eighth was on a previously unopacified middle cerebral artery. Thus the risk posed by these incidental aneurysms could be greater than is commonly appreciated, and since the morbidity of surgery has been much reduced with the advent of the dissecting microscope, it may be beneficial to operate on at least the more anatomically favourable of these aneurysms.

With our present policy, once an aneurysm responsible for subarachnoid haemorrhage has been shown to be amenable to direct surgery, or to be suitable only for medical treatment, there is no logical reason to proceed to more extensive angiography. Now computer-assisted transverse axial tomography (CAT) is known to be successful in showing intracranial haematomas, cerebral oedema and infarction (Ambrose, 1973; Hounsfield, 1973; Baker *et al.*, 1974; Paxton and Ambrose, 1974; Scott *et al.*, 1974). In some cases of clinical subarachnoid haemorrhage where the bleeding has occurred directly into the subarachnoid space the preangiographic localization of haematomas or the regional distribution of subarachnoid blood may be helpful in determining the site or at least the side of origin of the bleeding. In other cases blood in the cerebrospinal fluid is due to extension of silent intracerebral haemorrhage which can be localized easily on CAT.

We present the result of CAT in a small series of patients with subarachnoid haemorrhage, mainly to decide on its value in preangiographic localization of the bleeding site. If this can be established with reasonable certainty by atraumatic means, the angiographer could concentrate on detailed study of the appropriate region in suitable cases, provided that the policy of not actively treating incidental aneurysms continues to be approved. Since the basis of this policy is the assumption that incidental aneurysms rarely bleed and the literature on this point is ambiguous, we considered that an analysis of the subsequent clinical course of our patients with multiple aneurysms discovered during angiography for subarachnoid haemorrhage would be of interest.

Materials and Methods

One hundred patients with multiple aneurysms were traced by analysis of the angiograms of 667 consecutive cases of SAH due to intracranial aneurysm. The number and locations of these multiple aneurysms were analysed. Displacement of vessels adjacent to an aneurysm, irregularity and multilocularity as well as relatively large size, and localized spasm were considered as evidence of bleeding when the angiograms were reviewed. All the cases were followed up to the present, or until death, and any incident suggesting rebleeding was recorded and carefully assessed.

In a separate series of 75 patients with proven subarachnoid haemorrhage CAT was performed at intervals varying from the day of the haemorrhage up to 90 days later. In three cases there were two separate haemorrhages, making 78 subarachnoid bleeds in all. Any haematomas, their position, whether local or dispersed throughout the subarachnoid space and the location of regions of cerebral ischaemia, which may give rise to areas of low density with an absorption coefficient less than 12 units were noted. Cerebral infarction resulting from severe ischaemia can only be definitely distinguished from oedema when serial follow-up scans are performed: we have arbitrarily classified a low-density area with a space occupying effect as oedema and one without swelling as an infarct on the initial scan. We also routinely recorded the ventricular size on CAT, by subjective assessment when the ventricles were obviously normal or dilated, but utilizing Evan's ratio in borderline cases and for comparison of serial studies in individual patients.

Angiograms were made in all but three of these patients and were assessed in the same way as the previous series. In all except three cases the angiograms were performed within 14 days of the first CAT. Results are set out in Tables I–X.

Discussion

In the multiple aneurysms follow-up series surgical treatment was confined to the aneurysm which had bled and was by direct occlusion of its neck when possible (59 cases). Very occasionally the aneurysm was wrapped, when, following exposure, its neck could not be occluded. Proximal anterior cerebral clipping was employed in a few anterior communicating aneurysms and common carotid ligation in eight cases with aneurysms close to the carotid bifurcation. The relatively low percentage of multiple aneurysms in the whole group (Table I) is at least partly accounted for by less than 20 per cent of the patients being subjected to vertebral angiography. It should be noted that the percentage of multiple aneurysms was nearly double when the posterior circulation was examined. It is likely therefore, that the number of aneurysms which were demonstrated (Table II) is considerably less than those actually present, that the total of 232 aneurysms in the 100 patients with multiple aneurysms is a minimum estimate, and that 14 is an especially low figure for those in the posterior fossa.

It has been claimed that it is possible to recognize the aneurysm which has bled with an accuracy of 95 per cent (McKissock *et al.*, 1964) so that the lack of definite angiographic localizing of features in 43 per cent of our cases (Table III) is unusually high. Although this did influence the treatment of some cases, it could not have affected the long-term prognosis of the incidental aneurysms and is not

TABLE I
INCIDENCE OF MULTIPLE ANEURYSMS

Total number of cases of subarachnoid haemorrhage due to aneurysm 677			
Carotid angiograms performed in	677	Multiple aneurysms shown in	69 (12·8%)
Vertebral angiography performed in	131 (19·5%)	Multiple aneurysms shown in	31 (23·6%)
Total cases	667	Multiple aneurysms	100 (15%)

TABLE II
PATIENTS WITH MULTIPLE ANEURYSMS

	Number of patients	Total number of aneurysms
Number of aneurysms		
2	76	152
3	19	57
4	4	16
7	1	7
Total	100	232
Distribution of aneurysms		
Supratentorial	100	218
Infratentorial also	14	14
Total	114	232

TABLE III
ANGIOGRAPHIC EVIDENCE OF SITE OF HAEMORRHAGE

	Local vessel displacement only	Large size, irregular wall or multiloculated aneurysm	Both features present	No localizing features
Supratentorial (86 patients) aneurysms only	7	30	19	30
Combined supra and infratentorial aneurysms (14 patients)	0	0	1	13
Total (100)	7	30	20	43

TABLE IV

Follow-up of multiple aneurysms

Period of follow-up: 1–18 years			
	Supratentorial aneurysms	Supra + infratentorial aneurysms	Total
1. Death within two months	29 cases: 19 before surgery 10 following surgery (direct clip or wrap)	5 cases: 2 before surgery 3 following surgery (direct clip or wrap)	34
2. Alive 1–18 years	52 cases: 43 treated by surgery (36 clips or wraps 7 carotid ligations) 9 without surgery	9 cases: 7 treated by surgery (all clips or wraps) 2 without surgery	61
3. Death between 1–18 years	5 cases: 4 treated by surgery (3 clips; 1 ligation) 1 without surgery	0 cases:	5
Total	86	14	100

TABLE V

Causes of the five deaths during follow-up period of 1–18 years after subarachnoid haemorrhage

No. of aneurysms	Treatment	Time of death	Cause	Age at death
2 aneurysms on angiogram	Carotid ligation	Death 3 years	Sudden, presumed SAH, no autopsy	42
2 aneurysms on angiogram	Aneurysm clipped	Death 4 years	From carcinoma cervix	69
2 aneurysms on angiogram	Aneurysm clipped	Death 4 years	Cause unknown, no autopsy	69
2 aneurysms on angiogram	No surgery	Death 13 years	From myocardial infarct	79
2 aneurysms on angiogram	Aneurysm clipped	Death 14 years	Cause unknown, no autopsy	66

TABLE VI

Prognosis in multiple intracranial aneurysms

Year since haemorrhage	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	(Average 7·2 years)
Number of patients	3	6	11	9	8	4	6	1	8	2	3	2	2	0	1	1	0	1	
Number of deaths		1	2									1	1						

relevant in the present context. It emphasizes the importance of other methods of localization of haemorrhage, especially CAT.

The poor immediate prognosis of subarachnoid haemorrhage (Table IV) is confirmed in this series, 34 cases dying within two months of the initial haemorrhage. The prognosis of the 66 cases surviving this period was reasonably good. Only five have died since the haemorrhage (Table V); in two of these the cause of death was completely unrelated and in two others it was uncertain, but did not follow an episode suggesting a sudden intracranial catastrophe. The remaining death, which occurred three years after carotid tie for a terminal carotid aneurysm, was sudden and was likely to have been due to a further bleed, but this could well have occurred from the same aneurysm which had bled previously. Thus only one of the deaths appears to have been due to intracranial haemorrhage and there has been no suggestion of haemorrhage in any of the surviving cases during an average follow-up of more than seven years (Table VI). McKissock *et al.* (1964) in 85 cases of multiple aneurysms had a similar high mortality (34 per cent) in the first six months following the initial bleed and a relatively low mortality (5 per cent) over the next four to five years. They considered that any rebleeding was usually from the aneurysm which had already bled.

Even though the results in these series are at variance with those previously quoted from Heiskanen and Marttila (1970) the combined figures suggest that the incidence of haemorrhage from incidental aneurysms is sufficiently small to justify our present conservative policy of not interfering with the majority of them, and, therefore, makes it reasonable to limit angiography to that necessary for proper treatment of the recently ruptured aneurysm.

Of our 78 haemorrhages in which CAT has been performed, 25 (Tables VII, VIII, IX and X) showed a local haematoma (Fig. 1), 19 others an haematoma with infarction or oedema around it (Fig. 2) and 12 infarction or oedema alone (Fig. 3). In one patient, who had previously had a cutaneous melanoma removed, multiple previously silent metastases were shown on the surface of both cerebral hemispheres. There was haemorrhage adjacent to one of them (Fig. 4). Angiography showed causative aneurysms in 31 and angiomatous malformation in 11 of these 57 subarachnoid haemorrhages in 54 patients. In 20 patients the aneurysm was single, but there was definite angiographic evidence that it had bled in only six of them. Each of the other 13

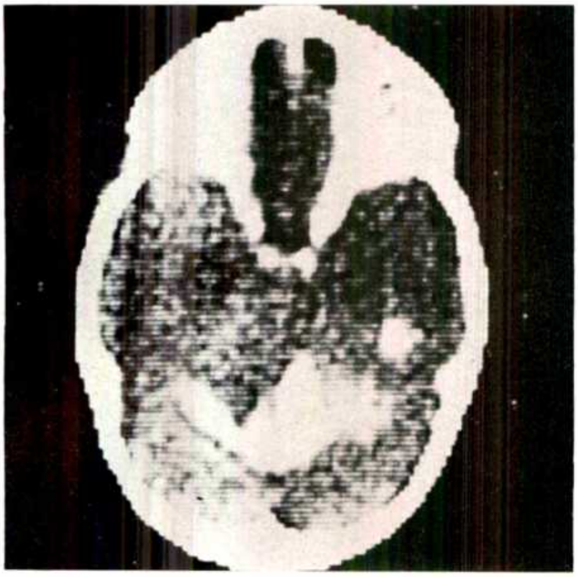
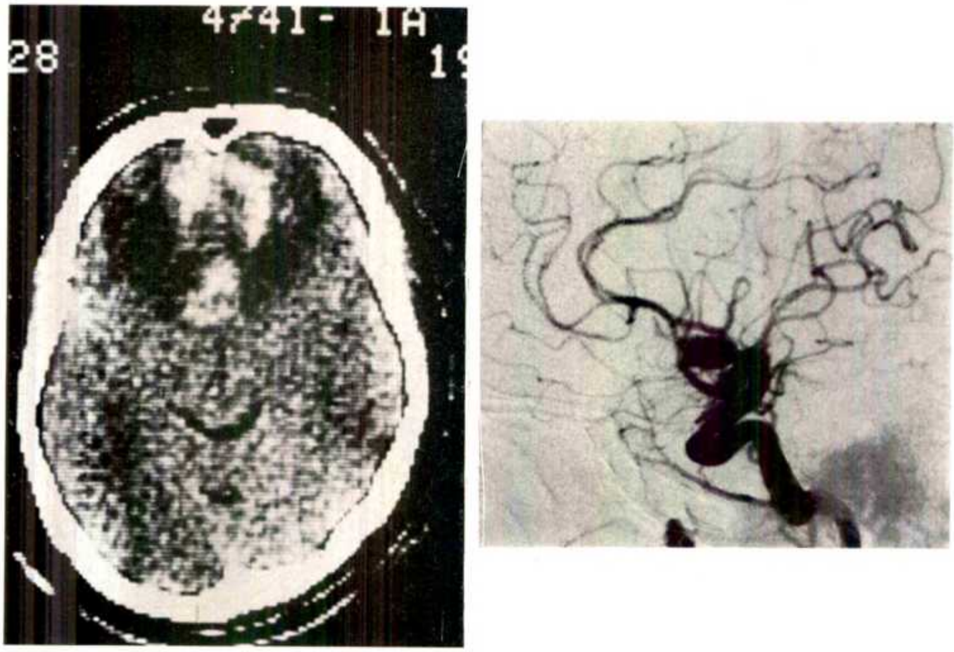


FIG. 1.

Tabel IX. Case 9. (N.P.)

CAT Note high-density area due to haemorrhage within the 4th ventricle and both cerebellar hemispheres. No angiograms were performed. Post-mortem confirmation.



A B

FIG. 2.

Table VII. Case 9. (G.W.)

(A) CAT, anterior communicating artery aneurysm. Note two areas of high density in the frontal region bilaterally and another high density area midline anterior to the 3rd ventricle due to sub and bifrontal haematoma. Two large low-density areas surround this lesion due to oedema-infarct in both frontal lobes.

(B) Left carotid angiogram demonstrating the anterior communicating artery aneurysm. There is separation of the anterior cerebral arteries below the genu by haematoma.

TABLE VII

SINGLE ANEURYSM SHOWN ON ANGIOGRAPHY

CAT findings						Angiographic findings			
Case No. and initials	Focal haematoma	Oedema/ infarct	Diffuse intraventricular or subarachnoid blood	Ventricular size	Days since bleed	Type	Location of aneurysm	Spasm	Localized mass on angiogram
1. K.N.	R. tempero-parietal	No	No	Small	1	R. carotid	R. middle cerebral	None	R. temporal
2. J.A.	R. anterio temporal	No	No	Moderate dilatation	1	B. carotid	R. posterior communicating	+	No
3. H.W.	No	R. hemisphere	+	12/39	1	4 vessels	R. anterior communicating	L. anterior cerebral	No
3a. H.W.	L. hemisphere and inter-hemispheric fissure	Bilateral parasagittal	+	14/38	6 (10)				
4. M.H.	Around L. sylvian fissure	No	No	Minimal dilatation	2	4 vessels	L. middle cerebral	None	No
5. K.E.	R. sylvian fissure	No	No	Dilated	2	4 vessels	R. posterior communicating	None	No
6.	L. medial-temporal	No	Subarachnoid and intraventricular	12/36	2	B. carotid	L. posterior communicating	None	L. medial temporal
7. A.S.	L. sylvian	No	No	Normal	2	4 vessels	R. middle cerebral	None	No
8. E.S.	L. temporal lobe	Oedema adjacent to clot	+	L. lateral ventricle dilated	3	B. carotid	L. posterior communicating	None	No
9. G.W.	Bilateral inferior frontal around aneurysm	Infarction both frontal lobes	No	L. occip. horn dilated otherwise normal	3	4 vessels	Anterior communicating	None	Subfrontal
10. N.S.	Suprasellar	No	+	Moderately dilated	3	4 vessels	Anterior communicating	None	No
11. J.R.	No	Parasagittal bilateral	No	9/35	3	4 vessels	L. anterior communicating	None	No
12. E.M.	R. temporal Lobe on to surface	R. hemisphere	No	L. lateral ventricle dilated	5	4 vessels	R. posterior communicating	None	R. temporal mass
13. L.D.	No	No	No	12/38	6	B. carotid	L. posterior communicating artery	None	No
14. C.S.	Subarachnoid over R. frontal convexity	R. frontal	No	5/37	6	B. carotid	L. posterior communicating artery	None	No

TABLE VII

SINGLE ANEURYSM SHOWN ON ANGIOGRAPHY—*continued*

CAT findings						Angiographic findings			
Case No. and initials	Focal haematoma	Oedema/ infarct	Diffuse intra-ventricular or subarachnoid blood	Ventricular size	Days since bleed	Type	Location of aneurysm	Spasm	Localized mass on angiogram
15. C.A.	L. frontal into corpus callosum	No	No	13/39	7	B. carotid	L. callosomarginal	None	No
16. G.M.	L. medial temporal	No	+	6/35	7	4 vessels	L. posterior communicating	None	No
17. J.H.	3rd ventricle posterior end	No	+	14/40	7	4 vessels	Terminal basilar	None	No
18. E.B.	No	No	No	Not measurable due to artefact	11	4 vessels	L. posterior communicating	None	No
19. I.W.	R. deep temporal extending into R. lateral ventricle	No	No	15/39	9	4 vessels	R. posterior communicating	None	No
20. L.P.	No	No	No	Slightly dilated	11	L. carotid	L. middle cerebral	None	No
21. J.W.	No	No	No	13/38	11	4 vessels	Anterior communicating	Left anterior cerebral	No
22. G.B.	No	No	No	5/38	11	4 vessels	L. internal carotid	L. supraclinoid carotid	No
23. R.A.	No	No	No	Dilated	12	4 vessels	R. posterior communicating	None	No
24. V.A.	No	L. fronto-parietal	No	Normal	14	4 vessels	L. middle cerebral	+	Parietal mass
25. V.H.	No	R. parietal	No	6/39	18	4 vessels	R. middle cerebral	None	No
26. F.W.	No	No	No	11/38	24	4 vessels	L. posterior communicating	None	No
27. N.A.	No	R. frontal	No	10/37	34	B. carotid	R. anterior cerebral-anterior communicating	None	No

TABLE VIII

Multiple aneurysms shown on angiography

CAT findings						Angiographic findings			
Case No. and initials	Focal haematoma	Oedema/infarct	Diffuse intraventricular or subarachnoid blood	Ventricular size	Days since bleed	Type	Location of aneurysm	Spasm	Localized mass on angiogram
1. V.H.	Interpeduncular cistern 3rd ventricle	Paraventricular bilat	+	14/36	0	4 vessels	Basilar R. posterior communicating	Terminal basilar posterior cerebrals	No
2. G.H.	L. sylvian	No	+	7/38	1	4 vessels	L. post. comm. L. mid. cerebral R. infraclinoid	None	No
2a.	L. temporal lobe	No	No	7/38	4 (5)				
3. P.T.	R. quadrigeminal cistern	No	No	Normal	1 (14)	B. Carotid	R. post. comm. R. ant. comm.	None	No
4. A.C.	R. temporal	No	No	Normal	1	4 vessels	R. ant. cerebral R. pericallosal B. internal carotid R. post comm.	None	R. temporal mass
5. M.V.	No	No	Intraventricular	Markedly dilated	2	4 vessels	R. terminal carotid L. supraclinoid	R. internal carotid + ant. cerebrals	No
6. D.G.	L. frontal lobe	Adjacent clot	No	Normal	2	B. carotid	L. middle cerebral R. middle cerebral	None	No
7. F.F.	No	R. hemisphere diffusely	+	7/37	3	4 vessels	R. internal carotid L. middle cerebrals	R. middle cerebrals	No
	No	Mature R. M. cerebral	No	9/37	60				
	No	Mature R.M.C.	No	11/36	365				
8. W.D.	No	L. parietal	No	Dilated	3	4 vessels	L. post cerebrals L. middle cerebral	None	No
9. M.C.	R. frontal	No	No	Normal	3	4 vessels	R. middle cerebral R. anterior cerebral L. P.I.C.A.	+	R. frontal swellling

TABLE VIII

MULTIPLE ANEURYSMS SHOWN ON ANGIOGRAPHY—*continued*

CAT findings						Angiographic findings			
Case No. and initials	Focal haematoma	Oedema/ infarct	Diffuse intraventricular or subarachnoid blood	Ventricular size	Days since bleed	Type	Location of aneurysm	Spasm	Localized mass on angiogram
10. M.A.	R. anterior deep temporal	R. temporal lobe	+	15/38	4	4 vessels	L. Ant. choroidal L. middle cerebral R. anterior cerebral R. interior carotid (2)	L. Ant. cerebral	No
11. E.P.	R. insula	Oedema R. temporal	No	9/32	5	4 vessels	R. middle cerebral	Middle cerebral	No
11a.	R. deep temporal	Oedema R. temporal	No	(L. normal (R. obliterated)	0		R. callosomarginal		
12. B.M.	No	No	No	Dilated	8	4 vessels	Anterior communicating B. middle cerebral (2 R; 1 L)	None	No
13. B.D.	No	No	No	11/40	8	4 vessels	R. middle cerebral terminal basilar	Posterior cerebrals	No
14. M.P.	No	No	No	11/36	11	B. carotid	B. middle cerebral R. Post Comm.	None	No
14a.	No	Oedema R. temporo-parietal	No	L. normal R. obliterated	Operation +3 (17)				
15. M.S.	R. medial temporal	No	No	14/38	14	B. carotid	R. internal carotid aneurysm Small L. internal carotid aneurysm	None	No
16. A.H.	No	No	No	Dilated	16	4 vessels	L. anterior comm. R. middle cerebral	Anterior cerebrals	No

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TABLE IX

NO SOURCE OF SUBARACHNOID HAEMORRHAGE SHOWN ON ANGIOGRAPHY

CAT findings						Angiographic findings			
Case No. and initials	Focal haematoma	Oedema/infarct	Diffuse intra-ventricular or subarachnoid blood	Ventricular size	Days since bleed	Type	Location of aneurysm	Spasm	Localized mass on angiogram
1. B.H.	No	R. frontal	+	10/40	1	4 vessels	—	None	No
2. T.F.	No	L. cerebellar	+	15/37	1	4 vessels	—	None	No
3. V.S.	R. temporo-parietal + intra-ventricular	Anterior to clot	No	L. dilated R. normal	1	R. carotid	—	None	R. temporo-parietal
4. E.F.	L. medial thalamus	No	No	Dilated	1	4 vessels	Aneurysms cervical carotids	None	No
5. C.W.	No	No	+	3/39	2	4 vessels	—	None	No
6. J.O.	No	No	+	10/38	2	4 vessels	—	None	No
7. P.R.	L. basal ganglia and lateral ventricle	No	No	Slightly dilated	2	4 vessels	—	None	Basal ganglia
8. G.W.	No	No	+	11/34	2	None— senile with generalized atheroma			
9. N.P.	B. cerebellar hemispheres and 4th–3rd ventricle	Inferior vermis	No	6/36 normal	4	None—decerebrate—died			
10. K.E.	L. frontal horn and adjacent frontal lobe	Adjacent oedema	No	10/37	5	4 vessels	—	None	No
11. K.J.	No	No	No	11/40	6	B. carotid	—	L. anterior cerebral L. middle cerebral	No
12. H.B.	No	R. frontal	+	8/38 normal	6	None—alcoholic—fractured skull. No history of trauma.			
13. J.L.	No	No	No	Dilated	8	4 vessels	—	L. anterior cerebral	No
14. E.P.	No	Bifrontal atrophy (old head injury)	No	15/42	9	4 vessels + spinal	— —	None None	No No
15. M.S.	No	R. temporal	No	Normal	11	4 vessels	—	None	No
16. G.C.	Medial R. temporal	R. temporal lobe	No	11/38	13	4 vessels	—	None	No
17. D.T.	No	No	No	10/40	25	4 vessels	—	None	No
18. L.M.	No	R. parietal	No	15/39	43	B. carotid	—	None	No

TABLE X

Angiomas shown on angiography

CAT findings						Angiographic findings			
Case No. and initials	Focal haematoma	Oedema/ infarct	Diffuse intra-ventricular or subarach-noid blood	Ventricular size	Days since bleed	Type	Location of aneurysm	Spasm	Localized mass on angiogram
*1. G.S.	Subfrontal R > L	No	+	14/37 dilated	0	B. carotid	Dural R. frontal and scalp	None	No
†2. K.W.	3rd ventricle and R. lat. ventricle	No	+	19/36 dilated	1	4 vessels	Choroid of 3rd ventricle	None	No
‡3. O.A.	R. temporo-parietal from convexity to ventricle	Slight round high density	Both lateral vents	12/41 normal	2	4 vessels	R. temporo-parietal	None	No
†4. N.G.	(Genu corpus callosum L > R) No	No	No	6/36 normal	2	4 vessels	Corpus callosum	None	No
†5. G.W.	L. temporo-parietal	Round clot	+	7/40 normal	2	L. carotid L. verte-bral	L. trigone	None	No
‡6. D.C.	R. thalamus	R. temporo-parietal	+	13/36 dilated	4	4 vessels	R. thalamus	None	Yes
†7. A.D.	R. occipital	No	+	7/38 normal	6	4 vessels	R. occipital	None	No
‡8. P.T.	L. cere-bellar with occluded 4th	Adjacent L cerebellar	No	14/42 dilated	7	Vertebral (bilateral)	L. cere-bellum	None	L. hemis-phere mass
‡9. C.R.	R. lateral ventricle	No oedoma	No	12/36 dilated	7	4 vessels	Wall of R. frontal horn	None	No
†10. E.S.	R. supra-ventricular white matter	R. pos-terior parieto-occipital	No	10/36 normal	14	4 vessels	R. parietal	None	Adjacent to angioma
†11. J.D.	L. high parietal up to convexity	No	No	normal	15	4 vessels	R. parietal	None	Adjacent to angioma
†12. A.M.	*(L. fronto-parietal)	Atrophy round previous surgical defect	No	10/38 dilated	49	L. carotid	L. fronto-parietal	None	No
†13. J.S.	R. occipital from medial surface to ventricle	No	No	normal	350	4 vessels	R. occipital	None	No

*No enhancement after i.v. Conray. †Enhancement. ‡Not enhanced.

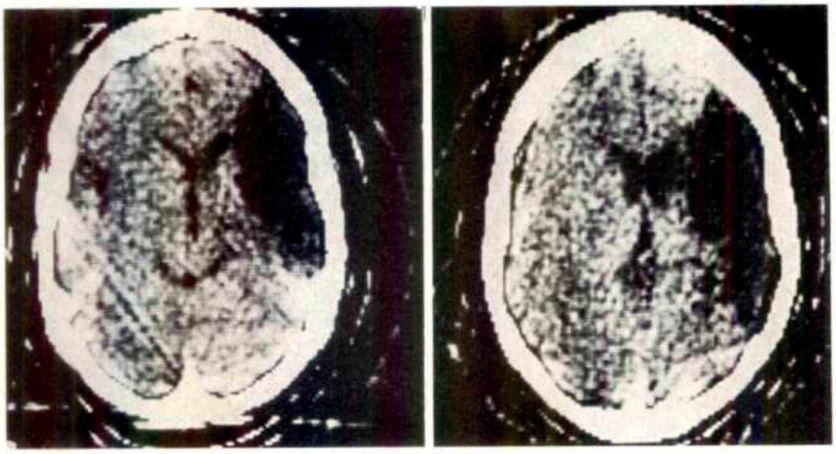


FIG. 3.
Table VIII. Case 7. (F.F.)
CAT, 60 days after bleed from right middle cerebral aneurysm. Note area of low density involving the right frontal, temporal and parietal lobes which represents a mature infarct within the right middle cerebral artery territory.

bleeds (11 patients) had two or more aneurysms (Fig. 5) and there was angiographic evidence of the site of haemorrhage in four of these. In one case a temporal haematoma shown on the EMI scan could potentially have arisen from either an ipsilateral posterior communicating or a middle cerebral aneurysm and angiographic evidence of spasm adjacent to the posterior communicating aneurysm was the only localizing feature. Two patients with local haematoma, three with haematoma plus oedema or infarction and four with infarction or oedema alone had no source of haemorrhage shown on angiography. In two other patients, in one of which a cerebellar haemorrhage was confirmed at post-mortem (Fig. 1) no angiograms were performed.

It is disappointing that 21 haemorrhages had no focal signs on unenhanced CAT. In two of these angiomatous malformations were shown after enhancement and it is evident from Table X that all our angiomatous malformations showed some abnormality on CAT (Fig. 6). It can be seen from Tables VII, VIII and IX that when CAT was performed within seven days of the haemorrhage, localized blood clot or low density due to oedema or infarction was present in 86 per cent; after this time localizing features were present in only 38 per cent. Fifteen of the 19 unlocalizing scans were performed after the first week, so it is likely that earlier studies would have been more rewarding. There was no evidence of a focal lesion in any examination including angiography in six of them; in one senile patient angiography was omitted. The other 12 had aneurysms, but in none of them, nor in the two patients with angiomatous malformations was there any mass lesion; in five there was localized arterial spasm.

Most aneurysms responsible for subarachnoid haemorrhage are small, situated close to the skull base, and contain fluid blood which has a density similar to brain substance. Therefore, they are not usually visualized on CAT. Sometimes, when they are of large size or contain clotted blood, or have calcified walls they are shown (Fig. 7). We have not rescanned after intravenous contrast routinely, but it has proved useful in confirming eight of the nine angiomatous malformations in which it has been used (Fig. 8), and four aneurysms presenting with subarachnoid haemorrhage have definitely enhanced (Fig. 9).

In our series of 75 cases of subarachnoid haemorrhage it was possible to localize or at least lateralize the site of haemorrhage by CAT alone in 56 patients. In these the angiographer would have been able to direct his attention to detailed study of the vessels in the region of the haemorrhage, utilizing magnification and subtraction and multiple projections as necessary for complete elucidation or exclusion of any detectable source of haemorrhage.

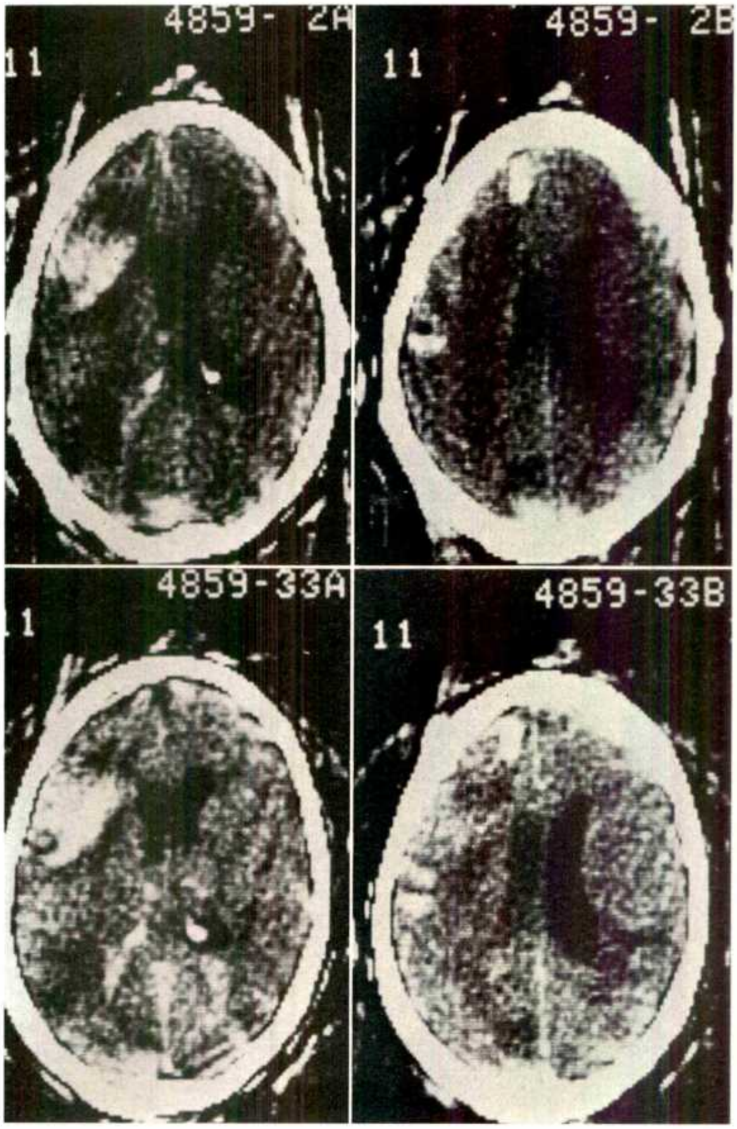
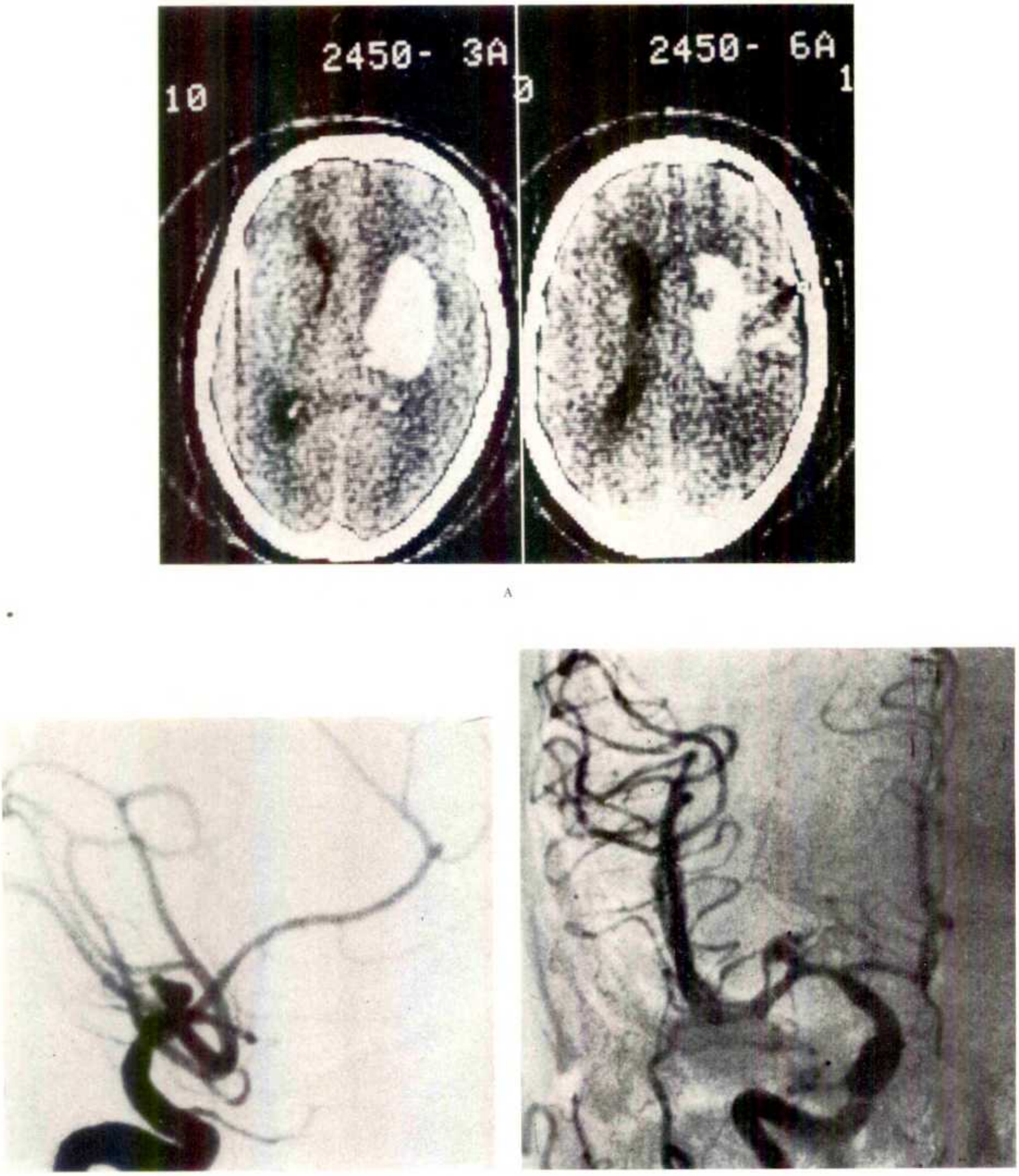


FIG. 4.

CAT, deposits from a cutaneous melanoma. Cuts 2A and 2B multiple peripheral areas of high density in the left frontal lobe. Cuts 33A and 33B following intravenous injection of 60 c.c. Conray new areas of increased density are evident and enhancement has occurred in others. Part of the large density is due to haemorrhage into a deposit.



A

B

C

FIG. 5.
Table VIII. Case 11. (E.P.)

(A) CAT, note high-density area deep in the right temporal lobe with marked shift from right to left of the midline structures. A low density area surrounds the lesion representing oedema of the adjacent brain.

(B) Magnified ×2 lateral. (C) Antero-posterior projections.

Right carotid angiogram demonstrating a right middle cerebral artery aneurysm associated with some spasm and a small right calloso-marginal artery aneurysm. The site of haematoma and of the spasm indicates bleeding from the middle cerebral aneurysm.

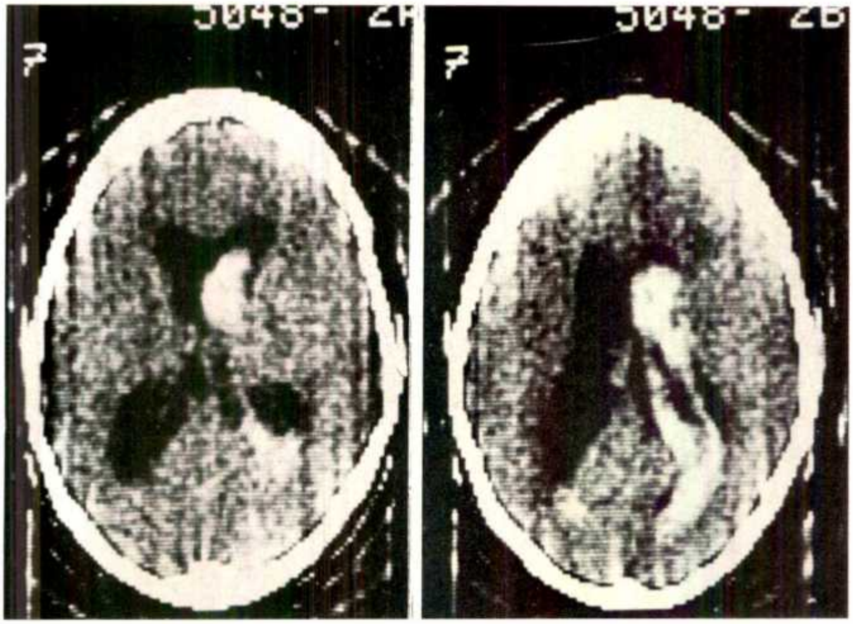
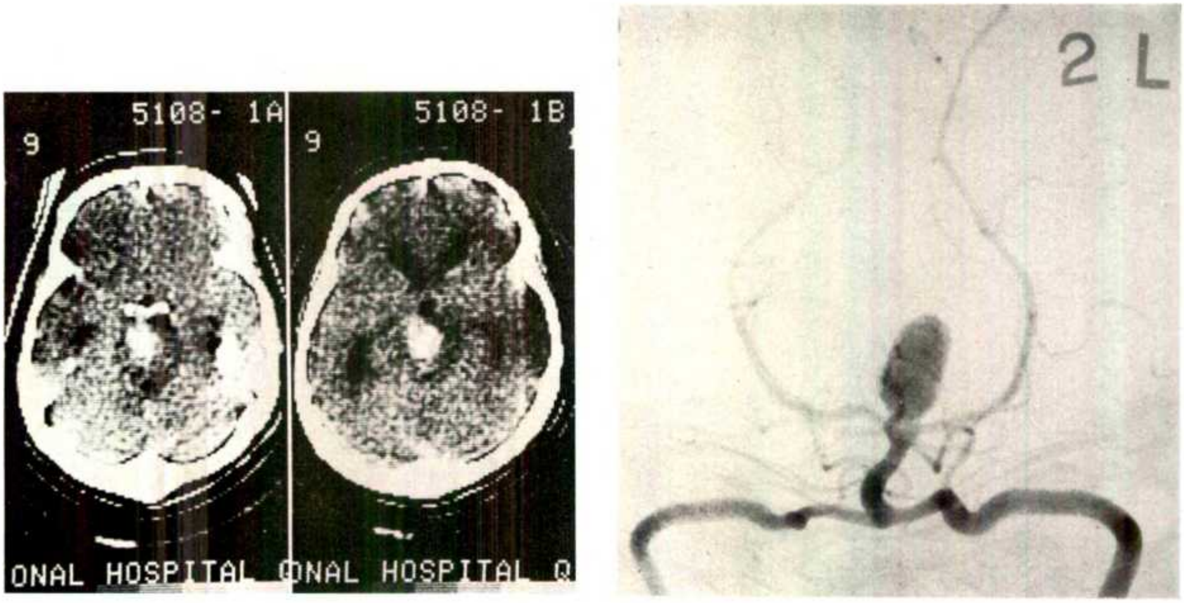


FIG. 6.
Table X. Case 9. (C.R.)

CAT, intraventricular angiomatous malformation. Localized high density area in the frontal horn and body of right ventrical due to angioma and blood clot. Blood clots present in trigone and occipital horns of ventricle and at tip of left occipital horn.



A

B

FIG. 7.
Table VII. Case 17. (J.H.)

(A) CAT terminal basilar aneurysm. Note high density in the midline on unenhanced scan due to the aneurysm. It projects into interpeduncular fossa and hypothalamus.

(B) Left vertebral angiogram demonstrating the basilar aneurysm.

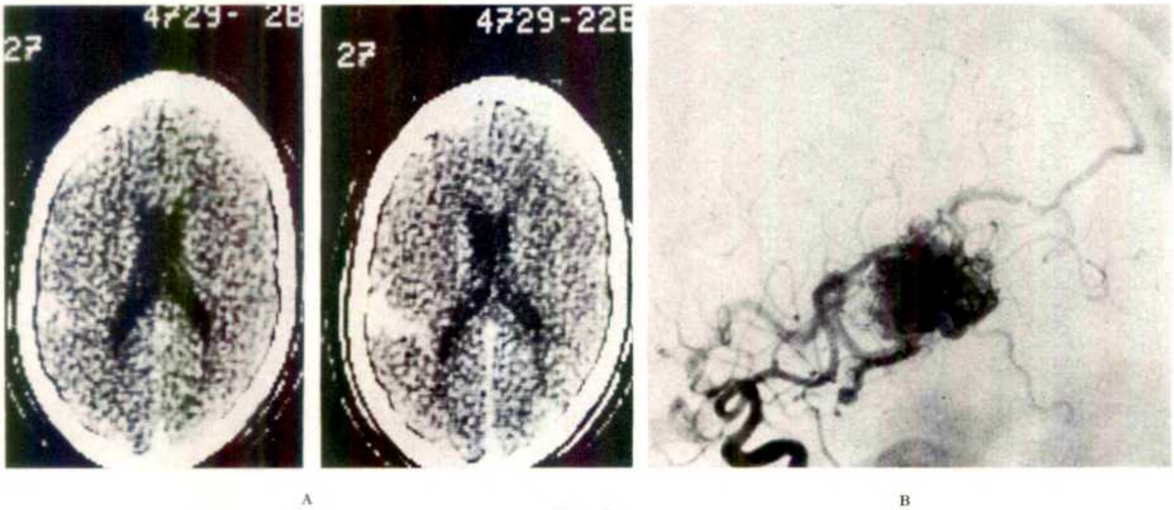


FIG. 8.

(A) CAT, angiomatous malformation in the left tempero-parietal region. Note a slightly high-density area (cut 2B) over the left tempero-parietal region which enhances following 60 ml. intravenous Conray (cut 22B). EMI units are in the range of 25–28.

(B) Left carotid angiogram demonstrates angiomatous malformation fed bythe left middle cerebral artery.

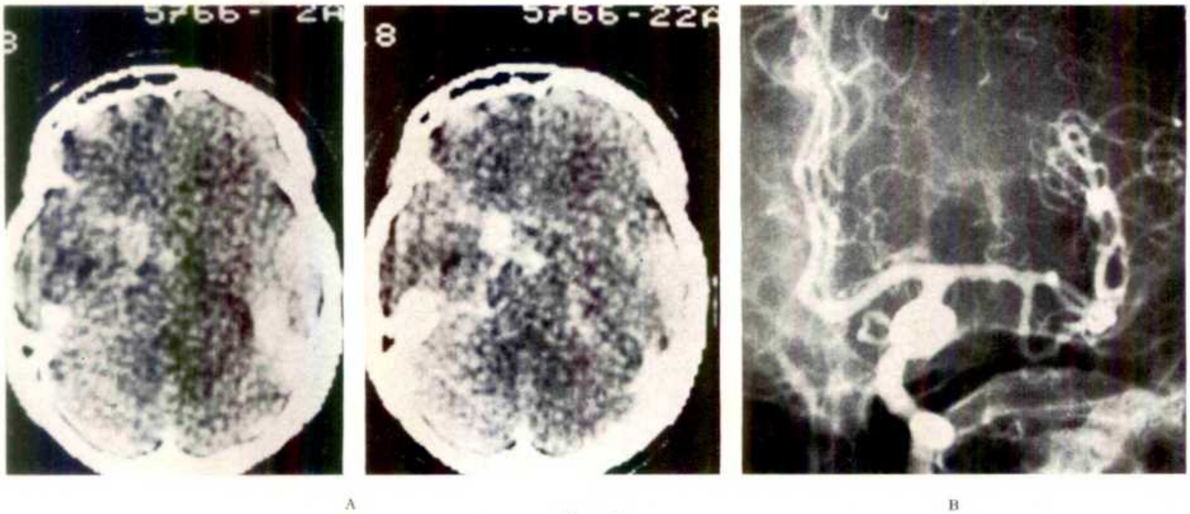


FIG. 9.
Table VIII. Case 16. (G.M.)

(A) Left posterior communicating aneurysm. Note high density area in cut 2A in the medial aspect of left temporal lobe due to the aneurysm. Cut 22A following 60 ml. i.v. Conray. The aneurysm has enhanced. The circle of Willis, middle and posterior cerebral arteries are visible.

(B) Antero-posterior left carotid angiogram demonstrating posterior communicating eneurysm.

When indirect surgery is contemplated the extent of further angiography is determined by the information required concerning collateral circulation and the presence or absence of vascular disease and incidental aneurysms. In no case in which a source of haemorrhage has not been found near the CAT abnormality has a relevant lesion been shown elsewhere on complete angiographic study, so that it would not appear to be necessary to pursue such extensive angiography in future cases. When atraumatic tests are negative the usual angiographic method of localizing the site of SAH is pursued.

Though not strictly relevant to the present thesis, the tables reveal further points of interest regarding CAT. Subarachnoid blood (Fig. 10) has occasionally been visible up to nine days after the recorded time

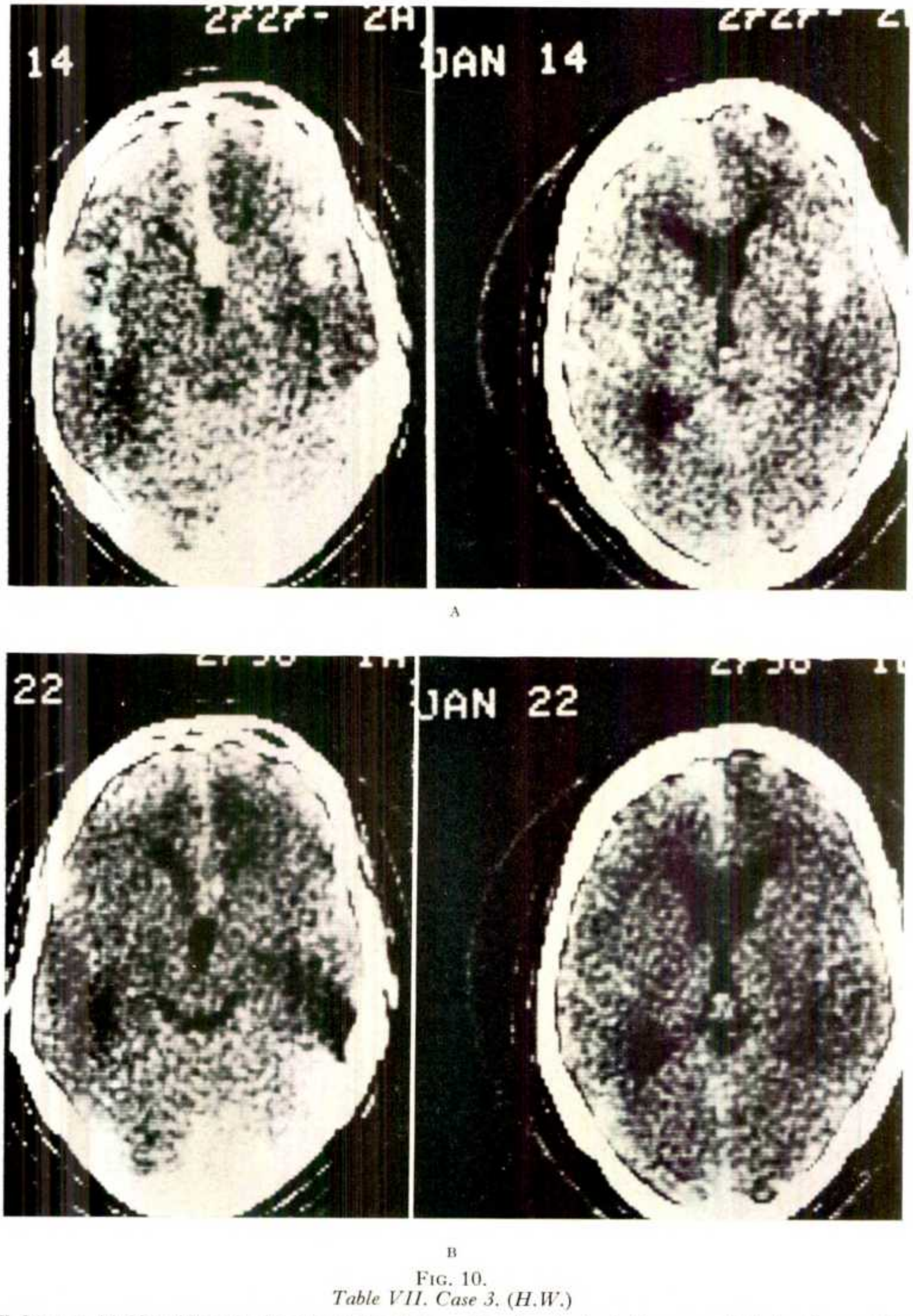
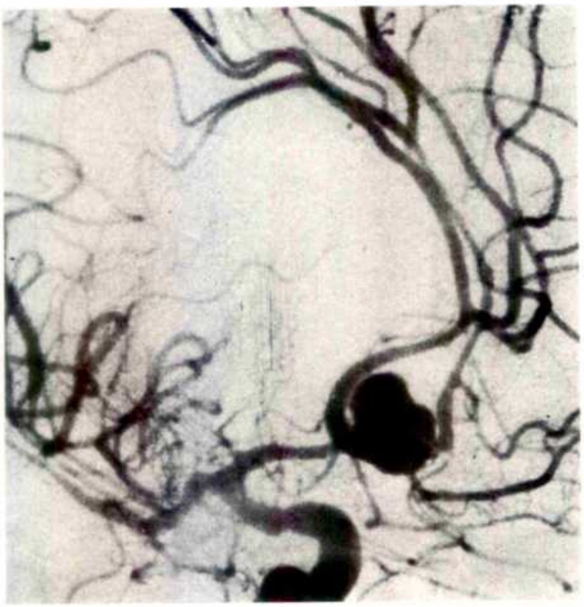


FIG. 10.
Table VII. Case 3. (H.W.)

(A) CAT, January 14. Note blood in the subarachnoid space (interhemispheric fissure and Sylvian fissure bilaterally).
(B) Second scan performed January 22, demonstrating partial resolution of the haemorrhage.



c

Fig. 10.
Table VII. Case 3. (H.W.)

(c) Right carotid angiogram demonstrating a large right anterior communicating artery aneurysm.

of haemorrhage, though it is not possible to exclude rebleeding in such cases. It is frequently visible in the first few days, but is not necessarily shown when the CSF is bloody and its absence manifestly is in no way helpful in excluding a subarachnoid haemorrhage. The range of pathology recognizable on CAT is most helpful in the elucidation of causes of change in the clinical state both before and after surgery. Unusual causes of haemorrhage such as previously silent tumours are easily shown, whereas previously intraventricular tumours in particular were sometimes not discovered until an encephalogram was performed for progression of the lesion at a later stage. The ventricular size is reliably shown and deterioration in the clinical state due to hydrocephalus, recurrent haemorrhage or infarction is readily distinguished at any time during the pre- or post-operative course.

Conclusion

Follow-up study of patients who have survived for two months following a subarachnoid haemorrhage and who have been shown to have multiple aneurysms suggests that bleeding from the incidental aneurysms is uncommon and that it is a reasonable policy not to perform elective surgery on the large majority of such aneurysms. Atraumatic studies, especially CAT performed within the first week after a subarachnoid haemorrhage shows a localizing or lateralizing abnormality in a large proportion of cases. We suggest that if the site of haemorrhage can be approximately localized prior to angiography, the latter should be directed primarily towards detailed demonstration of the vessels adjacent to the CAT abnormality, and extended to give any information relevant to surgical treatment. Further angiographic investigation to discover incidental aneurysms which have not bled is unnecessary, unless elective surgery on such lesions is contemplated.

Acknowledgment

We wish to thank Professor George du Boulay for making available material on the earlier cases of multiple aneurysms, and for his helpful advice.

References

Allcock, J. M., and Drake, G. G., 1965. Ruptured intracranial aneurysms – the role of arterial spasm. *Journal of Neurosurgery*, *22*, 21–29.

Ambrose, J., 1973. Computerized transverse axial scanning (tomography): Part 2. Clinical application. *British Journal of Radiology*, *46*, 1023–1047.

Baker, H. L., jun., Campbell, J. K., Houser, O. W., Rees, D. F., Sheedy, P. F., and Holman, C. B., 1974. Computer assisted tomography of the head: and early evaluation. *Mayo Clinic Proceedings*, *49*, 17–27.

BRAWLEY, B. W., STRANDNESS, D. E., jun., and KELLY, W. A., 1968. The biphasic response of cerebral vasospasm in experimental subarachnoid haemorrhage. *Journal of Neurosurgery, 28,* 1–8.

DU BOULAY, G. H., 1963. Distribution of spasm in the intracranial arteries after subarachnoid haemorrhage. *Acta Radiologica: Diagnosis, 1,* 257–266.

1965. Some observations on the natural history of intracranial aneurysms. *British Journal of Radiology, 38,* 721–757.

FLETCHER, T. M., TAVERAS, J. M., and POOL, J. L., 1959. Cerebral vasospasm in angiography for intracranial aneurysms. Incidence and significance in one hundred consecutive angiograms. *Archives of Neurology, 1,* 38–47.

GOLDSTEIN, S. L., 1967. Ventricular opacification secondary to rupture of intracranial aneurysm during angiography: case report. *Journal of Neurosurgery, 27,* 265–267.

GRIFFITH, H. B., CUMMINS, B. H., and THOMSON, J. L., 1972. Cerebral arterial spasm and hydrocephalus in leaking arterial aneurysms. *Neuroradiology, 4,* 212–14.

HEINZ, E. R., 1973. *Complications and legal implications of radiologic special procedures.* Edited by T. E. Meaney, A. F. Lalli, and R. J. Alfidi, p. 55 (G. V. Mosby Co).

HEISKANEN, O., 1965. The identification of ruptured aneurysm in patients with multiple intracranial aneurysms. *Neurochirurgia, 8,* 102–107.

HEISKANEN, O., and MARTTILA, I., 1970. Risk of rupture of a second aneurysm in patients with multiple aneurysms. *Journal of Neurosurgery, 32,* 295–299.

HOFF, J. T., and POTTS, D. G., 1969. Angiographic demonstration of haemorrhage into the fourth ventricle: case report. *Journal of Neurosurgery, 30,* 732–735.

HOUNSFIELD, G. N., 1973. Computerized transverse axial scanning (tomography): Part 1. Description of system. *British Journal of Radiology, 46,* 1016–1022.

JAMIESON, K. G., 1954. Rupture of an intracranial aneurysm during cerebral angiography. *Journal of Neurosurgery, 11,* 625–628.

KATSIOTIS, P. A., and TAPTAS, J. N., 1968. Embolism and spasm following subarachnoid haemorrhage. *Acta Radiologica: Diagnosis, 7,* 140–144.

KRICHEFF, I. I., CHASE, N. E., and RANSOHOFF, J. R., 1964. The angiographic investigations of ruptured intracranial aneurysms. *Radiology, 83,* 1016–1025.

LOCKSLEY, H. B., 1969. *Intracranial aneurysm and subarachnoid haemorrhage. A cooperative study.* Edited by A. L. Sahs, G. E. Perret, H. B. Locksley, and H. Nishioka, p. 143 (J. B. Lippincott Co., Philadelphia).

MCKISSOCK, W., RICHARDSON, A., WALSH, L., and OWEN, E., 1964. Multiple intracranial aneurysms. *Lancet, 1,* 623–626.

MARSHALL, W. H., JR., 1973. Delayed arterial spasm following subarachnoid haemorrhage. *Radiology, 106,* 325–327.

PAXTON, R., and AMBROSE, J., 1974. The EMI-Scanners. A brief review of the first 650 patients. *British Journal of Radiology, 47,* 530–565.

PERRETT, L. V., and BULL, J. W. D., 1959. III. The accuracy of radiology in demonstrating ruptured intracranial aneurysms. *British Journal of Radiology, 32,* 85–92.

POOL, J. L., JACOBSON, S., and FLETCHER, T. A., 1958 Cerebral vasospasm—clinical and experimental evidence. *Journal of the American Medical Association, 167,* 1599–1601.

POOL, J. L., and POTTS, D. G., 1965. *Aneurysms and arteriovenous anomalies of the brain: diagnosis and treatment* (Harper and Row, N.Y.).

SAHS, A. L., PERRETT, G. E., LOCKSLEY, H. B., and NISHIOKA, H., Editors, 1969. *Intracranial aneurysm and subarachnoid haemorrhage. A cooperative study.* (J. B. Lippincott Co., Philadelphia).

SCOTT, W. R., NEW, P. F. J., DAVIS, K. R., and SCHNUR, J. A., 1974. Computerized axial tomography of intracerebral and intraventricular haemorrhage. *Radiology, 112,* 73–80.

SYMON, L., DU BOULAY, G. H., ACKERMAN, R. H., DORSCH, N. W. G., and SHAH, S. H., 1973. The time-course of blood-induced spasm of cerebral arteries in baboons. *Neuroradiology, 5,* 40–42.

WAGA, S., KONDO, A., MORITAKE, K., and HANDA, H., 1973. Rupture of intracranial aneurysm during angiography. *Neuroradiology, 5,* 169–173.

WOOD, E. H., 1964. Angiographic identification of the ruptured lesion in patients with multiple cerebral aneurysms. *Journal of Neurosurgery, 21,* 182–198.

Book review

X-ray Equipment for Student Radiographers. By D. Noreen Chesney and Muriel O. Chesney, pp. 579, 2nd edn., 1975 (Blackwell Scientific Publications), £8·75.

Diagnostic X-ray equipment, over the past five years, has become more automated, and the radiographer has decidedly entered the "pushbutton age" brought about by the development of electronic circuitry. The authors of this well known text-book, taking this and other developments into account, decided that a second edition should be published. Among the new material is a chapter entitled "Logics" which is, they explain, in the context of X-ray equipment, "associated with the design of a computer system or unit". They explain how such a unit is now employed for the digital display of exposure factors and in exposure and radiographic timing and switching circuits. The explanations are simple, well written and clearly presented. The wider use of mammography has promoted the authors to include a new chapter on equipment used for this investigation.

As readers of the first edition will know, this is not a physicist's text-book, but is intended for the student radiographer, and hence complicated mathematical treatments are omitted. However, physicists and engineers, who are often ill informed concerning X-ray equipment, will find excellent lecture material in the text. The authors are to be congratulated on yet another worthwhile publication, both for the content and the clarity of presentation. This edition of the book will undoubtedly find a prominent place on the shelves of all who study radiography.

T. H. E. BRYANT.

1976, *British Journal of Radiology*, *49*, 502–515

Gas myelography in the investigation of occult spinal dysraphism

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(*Received January, 1975, and in revised form November, 1975*)

ABSTRACT

In patients presenting with suspected spinal dysraphism of the occult type, particularly children, cisternal gas myelography is coming to be accepted as the radiological investigation of choice. The technique of the examination as performed on 40 such patients is described in detail. There have been no complications. Twenty-five patients showed abnormalities of the cord together with low termination and abnormal fixation of the conus. The visualization was excellent in terms both of reliability and detail. The reasons for the difficulties in demonstrating these lesions using positive contrast and for preferring gas myelography are discussed.

There are few reports of the use of gas myelography in assessing congenital malformations of the spinal cord. This technique details the anatomy and pathology of the spinal cord with a clarity that cannot be matched by conventional positive contrast (oil) myelography, and thus provides the surgeon with more accurate preoperative information.

This paper describes the technique that has been used in the investigation of 40 consecutive patients with suspected spinal dysraphism of the occult type (Gryspeerdt, 1963). Certain hazards and technical difficulties are described and the procedure is evaluated as a means of investigating this group of conditions.

Spinal dysraphism is a term revived by Lichtenstein (1940) referring to developmental abnormalities in the midline of the back. In the occult forms there is no failure of development of the spinal cord, nor are there any associated anomalies of the brain. This group includes such conditions as diastematomyelia, diplomyelia, dermoid cyst or sinus, lipoma of the conus medullaris or filum terminale, and prolongation of the conus or its attachment by fibrous bands extending to the dura. These various entities often occur together, and may result in increased tension upon the cord and the nerve roots. They are associated with characteristic forms of clinical presentation, external stigmata and anomalies of the spine. These last features have been well described (James and Lassman, 1972) and their relationship in the present series of patients to the abnormalities shown at gas myelography is being described elsewhere (Cook, 1976).

TECHNIQUE

The exchange of 80–100 ml. of CSF with gas will define the spinal cord in an adult, particularly the level of its termination. 30–40 ml. will suffice in the youngest patients. The examination may last two hours and oxygen is absorbed inconveniently rapidly. If air were used the duration and degree of post-myelographic discomfort would be expected to be greater. For this reason a mixture of air and oxygen in equal amounts has been used. No system of pressure monitoring has been employed.

Apparatus

The earlier examinations were performed on a conventional tilting X-ray table with image amplification and television monitoring. A linear tomographic attachment was used. The later patients were examined using the Mimer III apparatus.

Method

Gryspeerdt (1963) stressed the importance of cisternal puncture in these patients to avoid possible injury to the spinal cord which may extend to an abnormally low level. In 36 of the 40 patients this route was used. In two patients investigated for cervical dysraphism the lumbar route was used. One further patient, a three-year-old girl, became apnoeic whenever the cisternal needle approached the dura, although this was not punctured. The examination was completed via the lumbar route with no further difficulties or subsequent ill effects. The cord, however, did extend to a low level in this child, and Fig. 1 illustrates the close proximity of the lumbar-puncture needle and demonstrates why cisternal puncture is normally to be preferred.

In a second girl, aged ten years, a cisternal puncture could not be performed, and again the lumbar route was used. In every patient the entire spinal cord has been outlined, and in many the 4th ventricle has also been seen. With the exception of the two cases of cervical dysraphism, no abnormality has been shown at the craniovertebral level. We should thus concur with Gryspeerdt (1963) that in contradistinction to meningomyelocoele there is no evidence of an association between occult spinal dysraphism and malformations of the Arnold-Chiari type that might make cisternal puncture hazardous. Nevertheless, the preliminary films should be examined to exclude, as far as possible, any chance association with a cervical anomaly. There were no complications of cisternal puncture; this was performed in all cases except one at the atlanto-occipital level. The remaining patient showed the posterior arch of the atlas to be in close apposition to the occiput, and the puncture was performed without difficulty at the atlanto-axial level.

Before the needle is removed a lateral film of the lumbar spine is obtained to ensure that enough gas has been introduced. The needle is then withdrawn and two lateral films are obtained to include the whole length of the spine. In the larger patients the

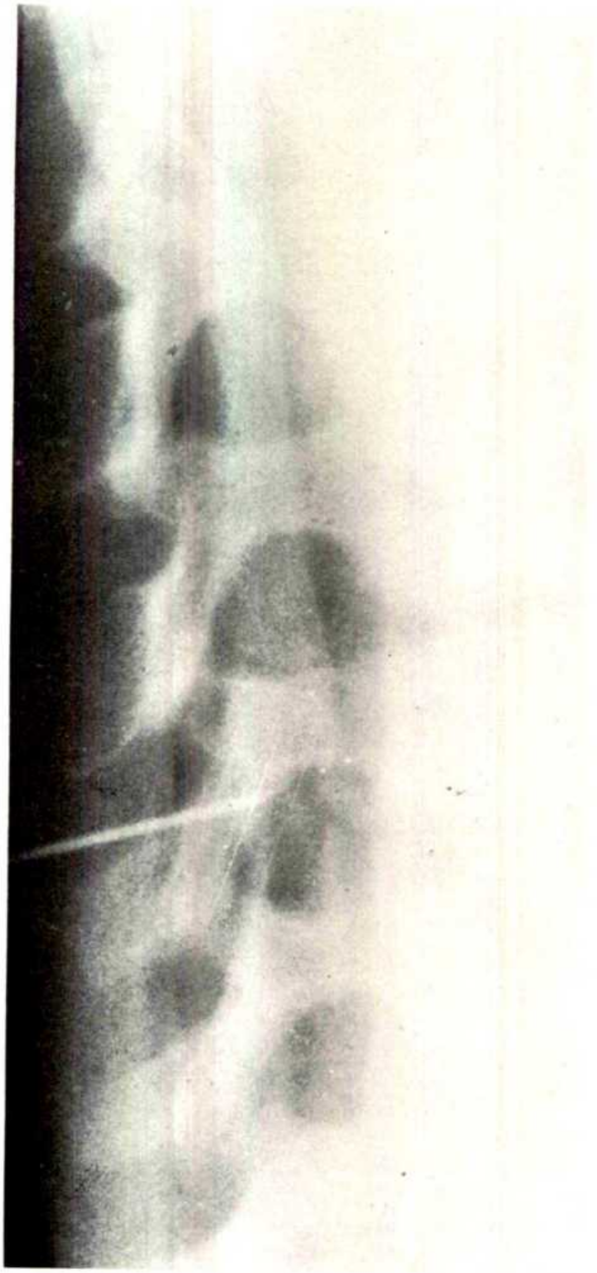

FIG. 1. *Case 11 E.T.*

Lateral tomogram of lumbar gas myelogram. The lumbar-puncture needle is shown *in situ* in close proximity to a low, expanded and tethered conus.

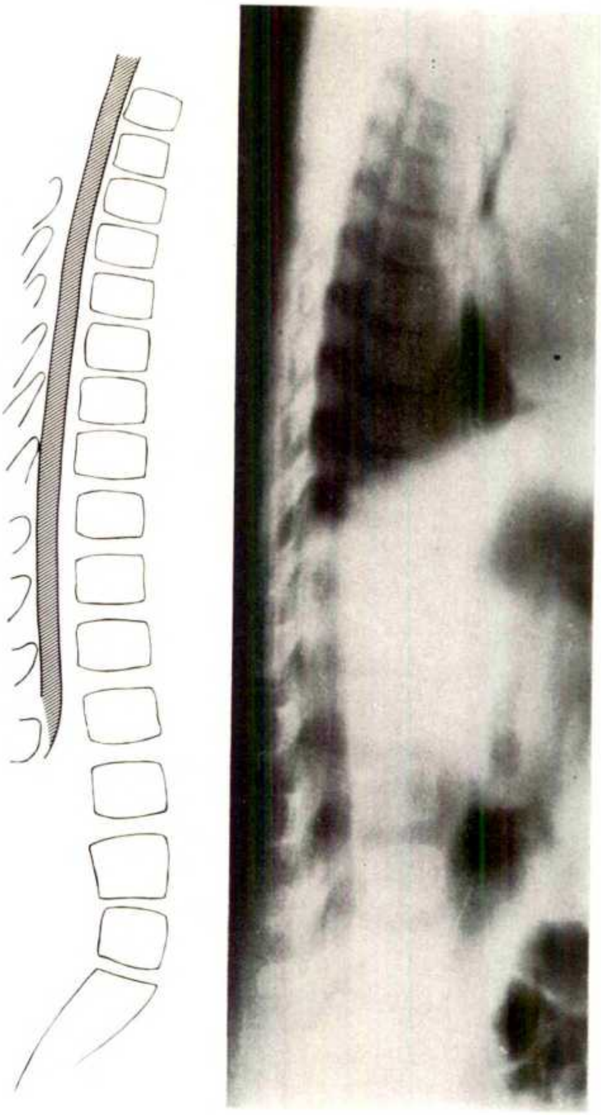

FIG. 2. *Case 6 A.M.S.*

Lateral tomogram of dorsilumbar gas myelogram. The cord is only minimally prolonged to the level of LV3 but it is adherent posteriorly and its mobility is restricted. These findings were confirmed at operation.

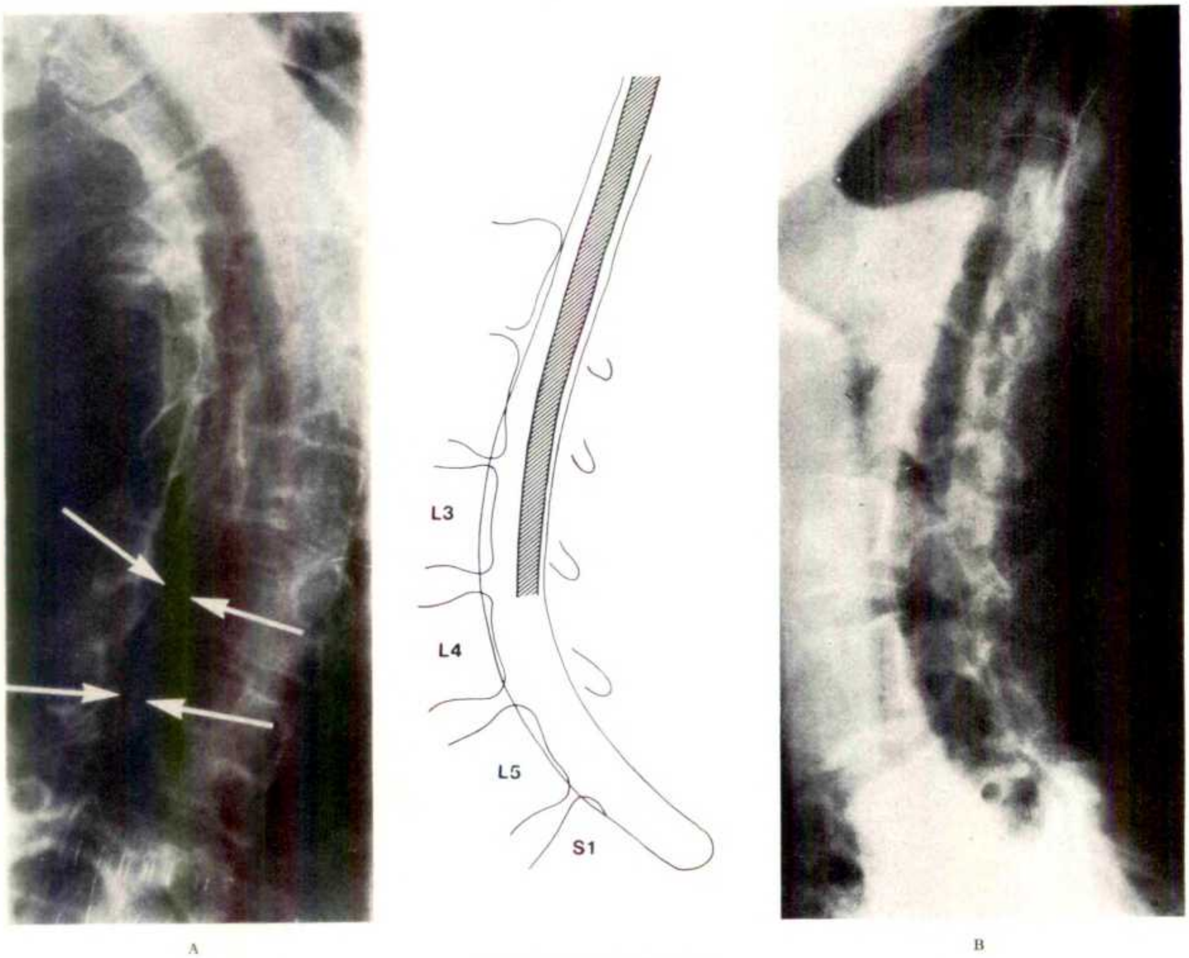

Fig. 3. *Case 22 S.T.* (A)

Antero-posterior view of lumbar gas myelogram. The conus ends at the level of LV3 and the original films show it to be split. A thickened filum extends from the conus (arrows). In spite of the scoliosis good definition has been achieved even without tomography.

Fig. 3. *Case 21 C.P.* (B)

Lateral view of lumbar gas myelogram. The low conus is well shown without need of tomography.

upper dorsal region may be inadequately shown and a film taken in slight obliquity may be necessary. Tomography of this region (Oden, 1953) has not been necessary. Unless specifically indicated the examination is now restricted to the lower end of the spinal canal and the following films are made:

(1) postero-anterior in the prone position, usually followed by

(2) and (3) both lateral decubitus positions using a horizontal X-ray tube.

Additional views may be required in some patients:

(4) and (5) "cross-table" lateral projections taken with the patient prone and supine.

(6) and (7) tomograms in the lateral and coronal planes.

These latter films are not made if the initial lateral and postero-anterior views show the cord clearly to end either at a normal level or at a very low level. In the latter situation the omission of the final films possibly involves some sacrifice of fine detail, but this is felt to be justified in the interest of reducing irradiation.

The normal cord quite commonly deviates to one side of the subarachnoid space at its lower end and its termination may then be difficult to see. It will however move across the subarachnoid space into a dependent position. The lateral decubitus and cross-table films will show the termination of the cord more clearly and define any restriction of its freedom to move. Tomography is seldom necessary

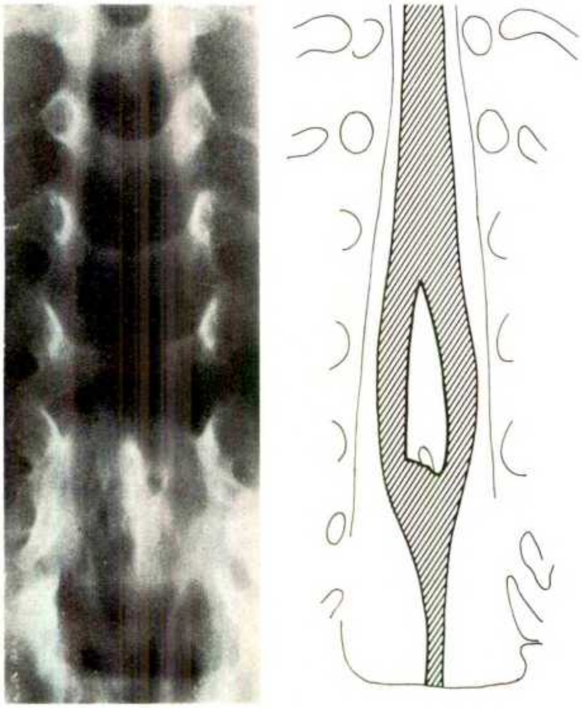

FIG. 4. *Case 1 C.C.*

Antero-posterior tomogram of lumbar gas myelogram. The cord is widely split and transfixed by a bony spur. Below the spur the separate components end at the level of LV4 in a mass with a further thickened prolongation below. At operation a complete diplomyelia was found and the mass was a mixed tangle of nerves and blood vessels.

but may be required in the coronal plane if definition is obscured by faecal shadows. In older patients it is required more frequently, and in scoliotic patients it may be needed in both planes for a clear demonstration of the relationships between the cord and the canal. This has, however, not always proved to be necessary. In the present series tomography has been used in 17 patients.

SERIES

Gas myelography, as described above, was performed on 40 consecutive patients with ages ranging between 14 months and 28 years in whom a diagnosis of occult spinal dysraphism was considered possible on clinical grounds. These patients presented either to the Wessex Neurological Centre or to the Southampton Children's Hospital between 1970 and 1974. One additional patient, a four-year-old boy, with obvious clinical dysraphism, presented with a history of nine illnesses suggestive of meningitis and did not therefore undergo myelography. Tethering bands and a dermoid cyst associated with a "lumbar epithelial fistulous tube" were found at operation. The four scoliotic patients were taken from a much larger group submitted for gas myelography prior to corrective orthopaedic treatment. These were the only patients in this larger group who showed external or plain film evidence of dysraphism in addition to the spinal abnormalities associated with the scoliosis. They were also the only patients with a scoliosis in whom myelographic evidence of dysraphism was found as opposed to the usual finding of a relatively short cord which passes along the concave aspects of the curving spinal canal (Roth, 1969).

Myelographic abnormalities were shown in 25 patients (Figs. 4–11), and surgical confirmation of the abnormality has been obtained in 22 of these. The abnormal findings are summarized in Table I

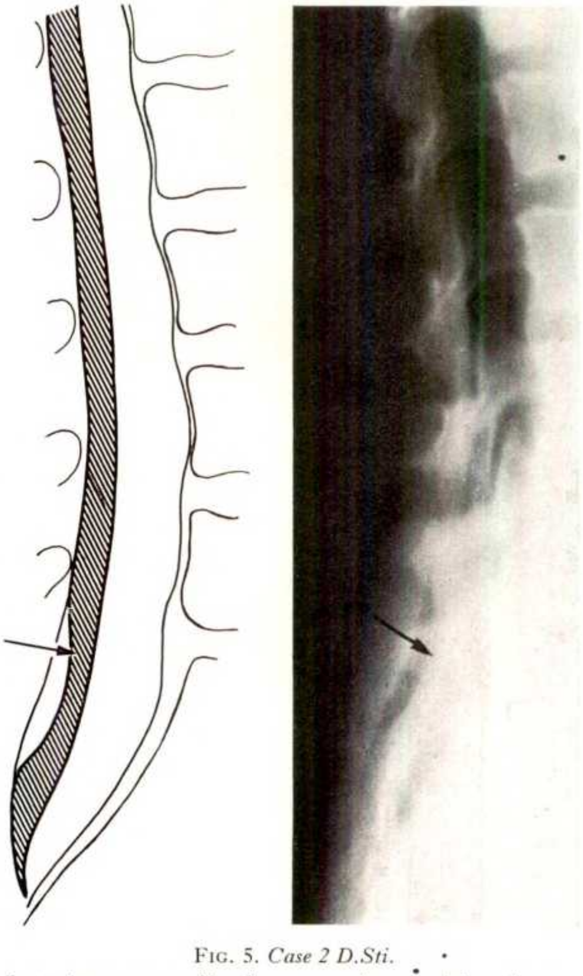

FIG. 5. *Case 2 D.Sti.*

Lateral tomogram of lumbar gas myelogram. A broad extension of the conus (arrows) ends in a mass. At operation the entire prolongation was found to be an elongated lipoma.

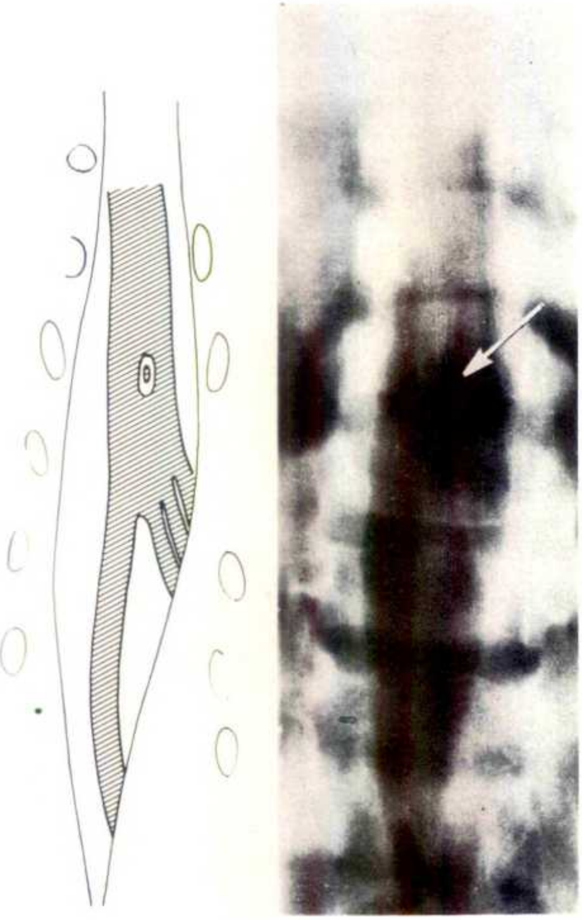

Fig. 6. *Case 3 Al.Sta.*

Antero-posterior tomogram of lumbar gas myelogram. The conus extends to the level of LV3 beyond which the filum is thickened. There is a small split in the conus (arrow) and a group of tethering bands pass to the left. There is restricted mobility of the conus from side to side. At operation these findings were confirmed.

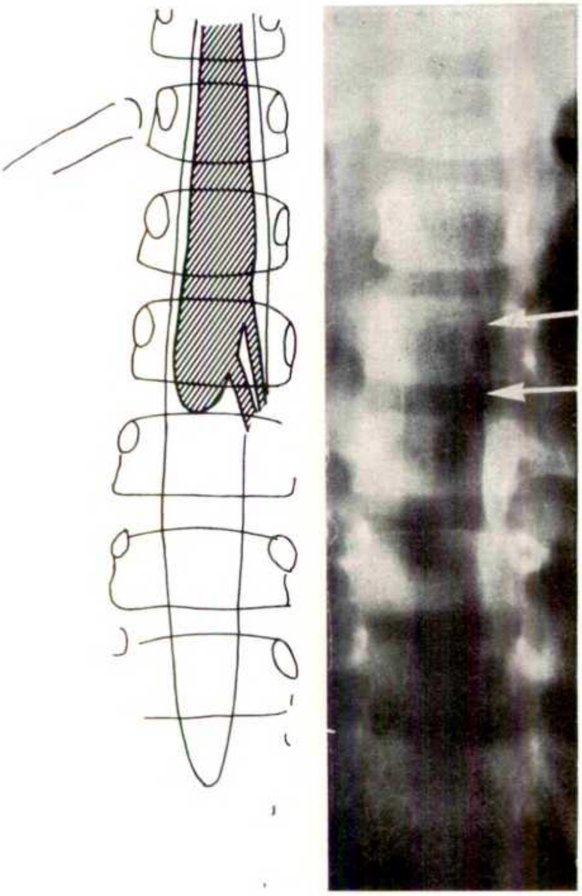

Fig. 7. *Case 4 L.H.*

Antero-posterior tomogram of lumbar gas myelogram. The cord ends at the level of the upper border of LV3 but the conus is enlarged and its mobility is restricted. Two bands pass from the expanded conus to the left (arrows). At operation an intramedullary lipoma was found and the bands blended into this.

and the operative correlation is given in Table II. These are considered further in the discussion. In most of these patients more than one abnormal feature was shown. In addition, two patients in whom no myelographic abnormality was described, nevertheless gave rise to such clinical suspicion of dysraphism that a laminectomy was performed and the dura opened; both were confirmed to be normal. There have been no other operations performed in confirmation of negative myelographic findings, but the subsequent clinical course of many of these patients has lent support to their not being cases of dysraphism. There was one false-positive myelogram (Fig. 12). In this patient, a girl aged nine who had recently developed enuresis, the conus was clearly seen ending at the level of the 1st lumbar vertebra. Below this there appeared to be a thick extension of the cord 0·6 cm wide passing nearly to the lumbosacral level. This was interpreted as an abnormally thickened filum terminale. At operation the components of the cauda equina were found to lie closely applied to each other in a number of thick bundles lightly bound together but with no evidence of tension. The conus medullaris and filum terminale were normal. This patient showed none of the characteristic external stigmata or spinal changes associated with occult dysraphism. Although these are not invariably present, the absence of both features

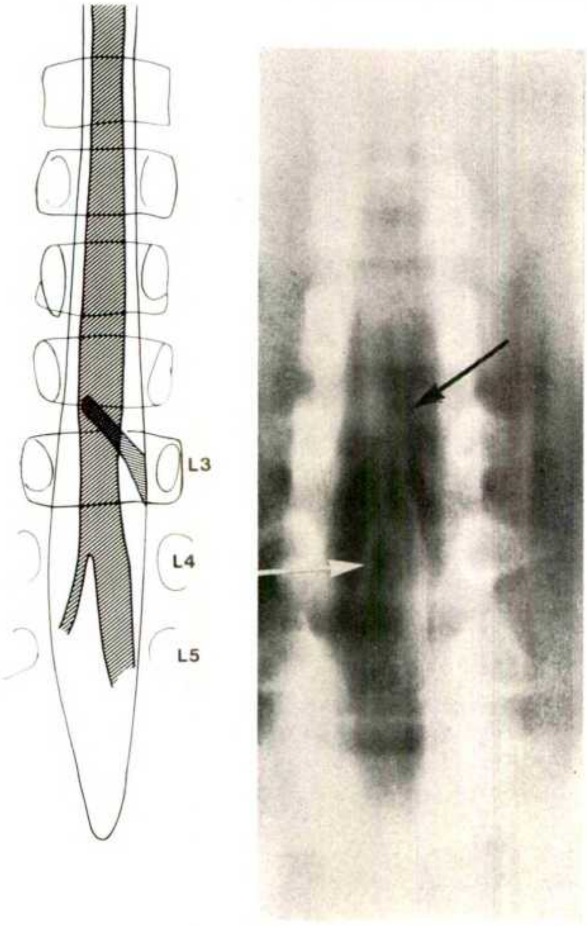

FIG. 8. *Case 7 D.C.*

Antero-posterior tomogram of lumbar gas myelogram. The conus extends at least to the level of LV4 with a further thickened band below this, but the exact level to which neural tissue extends could not be defined either at myelography or at operation. Two tethering bands are shown (arrows).

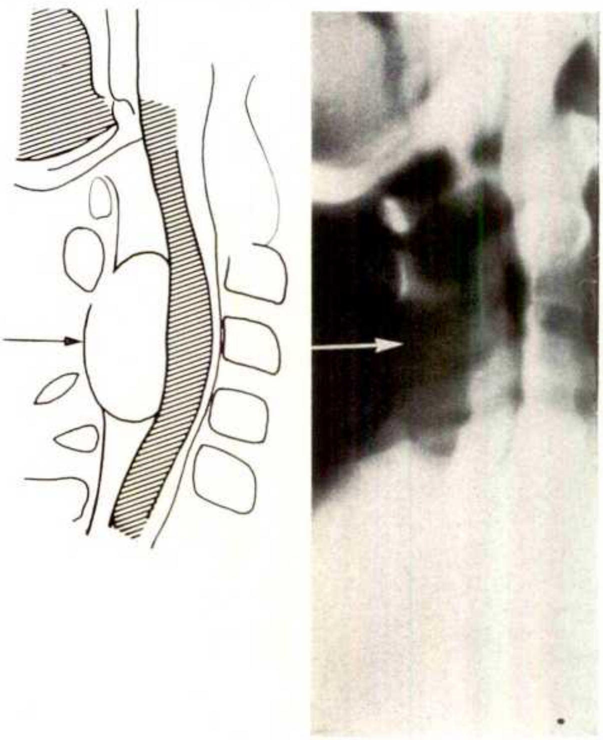

FIG. 9. *Case 8 D.Sto.*

Lateral tomogram of cervical gas myelogram. The cervical cord is displaced by a mass on its dorsal aspect (arrow). The cord is thin above the mass and there is widening and bony dysraphism of the spinal canal. At operation the mass was an enteric cyst containing gastric mucosal elements.

should compel very careful assessment of possible myelographic abnormalities. Perhaps greater attention to the mobility of the conus in this patient would have prevented this misinterpretation.

There are two patients in whom myelographic abnormalities have been defined, but no operation has been performed. In the first of these, a five-year-old boy with a typical deformity of the leg and foot and characteristic external and spinal abnormalities, the cord was shown to extend to the 3rd lumbar vertebra but to be freely mobile across an excessively wide subarachnoid space with no evidence of tethering bands or a thickened filum. It was considered very unlikely that a surgically remediable lesion would be found. The second patient, a girl aged seven, had recently developed incontinence and showed similar external and spinal abnormalities. The cord was shown to extend to the 3rd lumbar vertebra with restricted mobility and associated tethering bands. Unfortunately this child had undergone extensive operations to the back on three occasions in early life at another hospital for removal of the lumbosacral patch of hair. This had resulted in a large unsightly mass of scar tissue and her parents have preferred to delay an operation although she is kept under regular review.

DISCUSSION AND CORRELATION OF RESULTS

In most adults the tip of the conus lies at the level of the 1st lumbar vertebral body or the intervertebral disc below. In only 2 per cent of normal individuals does the spinal cord extend as far as the 3rd lumbar vertebra (Burrows, 1968). In the full-term fetus the cord terminates at the level of the 2nd lumbar vertebra and it reaches its final level within the first few months of life (Barson, 1970).

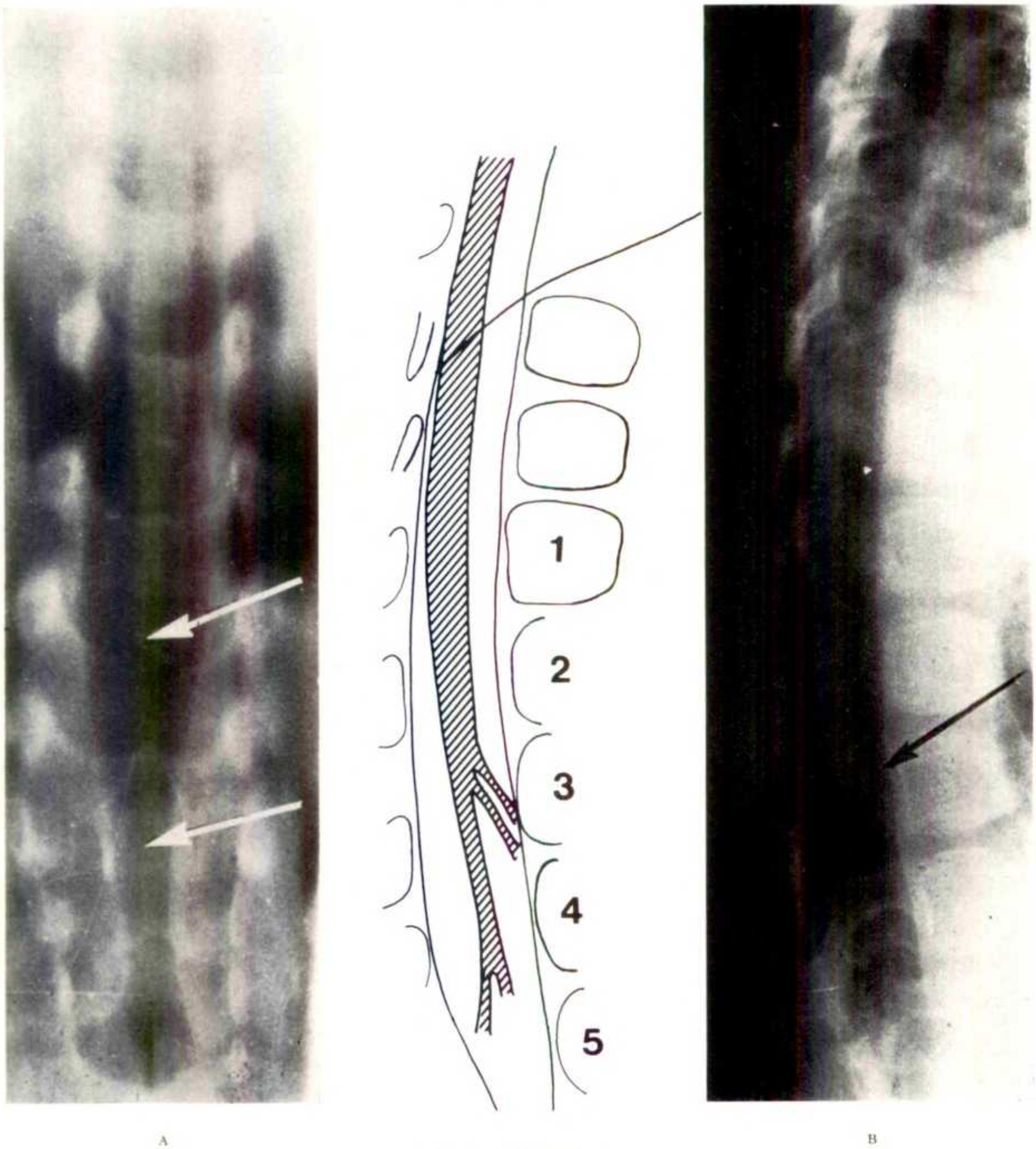

Fig. 10. *Case 9 D.W.*

(A) Antero-posterior tomogram of lumbar gas myelogram. The tapering conus ends at the level of the LV2/LV3 disc but a thickened extension (arrows) passes to the lower extremity of the subarachnoid space. This was considered to be an abnormally thickened filum and other films showed it to end in a small nodule. At operation this nodule was found to be a small lipoma which was tethering a cluster of strands which passed in a bundle to the conus but was separate from the filum.

(B) Lateral tomogram. The low termination of the cord and the thickened extension are again shown with some additional tethering bands anteriorly (arrow).

There is very little information available concerning the use of the technique in the investigation of this group of conditions. Lombardi and Passerini (1964) summarize the status of the examination as follows "The only condition in which gas contrast media are superior to positive contrast media is atrophy of the spinal cord". Valentino (1965) agrees and states that the limitations cannot help but dampen enthusiasm. Jirout (1969) dealing specifically with pneumomyelography makes no mention of dysraphism although he previously (1966) had described the use of this technique in evaluating mobility of the spinal cord. The classic work by Gryspeerdt (1963), James and Lassman (1972) and also nearly all published cases from The Hospital for Sick Children (Burrows, 1968; Till, 1968) were based on the use of positive contrast myelography using oil. Jones and Love (1956) illustrate a gas myelogram in a patient with a "tight filum terminale" in which the dural sac is pulled backwards without any deformity along the ventral aspect which might have suggested an extradural abnormality. Love *et al.* (1961) described three siblings with a similar diagnosis in whom the gas was seen to be displaced posteriorly at the lumbosacral junction. We have not seen significant dural displacements of this type in the present series. We should agree with Gryspeerdt (1963) that a localized increase in the distance between the posterior surfaces of the vertebral bodies and the anterior aspect

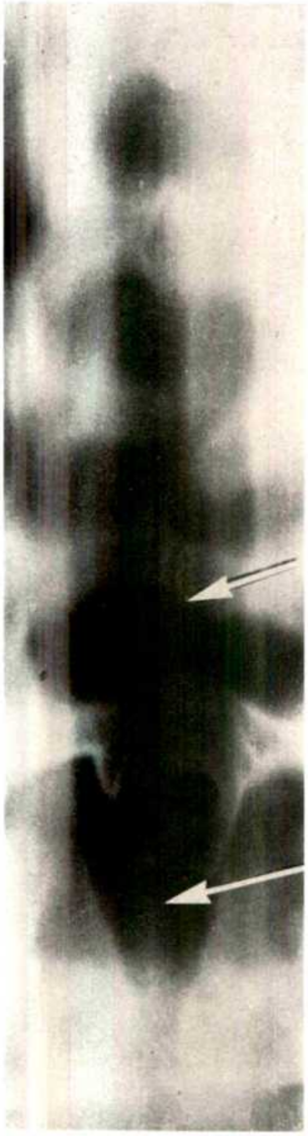

FIG. 11. *Case 10 M.T.*

Antero-posterior tomogram of lumbar gas myelogram. A thick strand (arrows) thought to be the filum extends from the conus to the level of S1. Note the characteristic defect in the bony lamina. At operation the entire strand was found to be an elongated lipoma, but the similar appearance to Fig. 10 should be noted.

TABLE I

SUMMARY OF ABNORMAL MYELOGRAPHIC FINDINGS CONFIRMED AT OPERATION

1. Level of termination of the conus	L2/3* L3 Below L3	7 9 } 18 9	25
2. Thickened extension below the conus			10
3. Tethering bands passing to the theca			15
4. Splitting of the cord or diplomyelia			5
5. Atrophy of the cord			2
6. Mass			3
7. Expansion of conus (intramedullary lipoma)			3

*In the presence of other abnormalities.
Gas myelography performed in 40 patients.
Gas myelography abnormal in 25 patients.
Laminectomy performed in 23 of the 25 abnormal patients confirming the abnormalities in 22.
Laminectomy performed in 2 of the 15 normal patients confirming the normal findings in both.

TABLE II

CORRELATION OF MYELOGRAPHIC AND OPERATIVE FINDINGS

Patient	Age	Sex	Scoliosis	Myelographic findings					Comments The operative findings confirm the myelographic findings unless otherwise stated.
				Cord inc. mobility	Level of conus	Thickened filum terminale	Tethering bands	Mass	
1. C.C.	2	Female	—	Widely split	L4	—	+	+	Diplomyelia. The "mass" consisted of a tangle of nerves and blood vessels.
2. D.Sti	10	Female	—	—	L4	+	—	+	The thick filum was an elongated lipoma.
3. Al.Sta.	4	Female	—	Restricted mobility	L3	+	+	—	The cord was found to have a small split although no spur passed through.
4. L.H.	3	Female	—	Enlarged conus Restricted mobility	L3	—	+	—	The tethering bands blended with an intramedullary lipoma of the conus.
5. H.G.	5	Female	—	Almost immobile	L4 adherent to theca	—	—	—	The termination was adherent as predicted. The level at at which neural tissue ended could not be defined.
6. A.M.S	4	Female	—	Restricted mobility	Upper L3 adherent posteriorly	—	—	—	Both the level of termination and the adherence were confirmed.
7. D.C.	10	Female	—	—	L4	+	+	—	The level to which neural tissue extended was impossible to define macroscopically.
8. D.Sto.	8	Male	—	Atrophic and displaced	L2	—	—	+	Cervical dysraphism. The mass was a "dorsal enteric cyst."
9. D.W.	14/12	Female	—	—	L2/3	+ ending in a small nodule	—	—	The "thickened filum" consisted of a cluster of strands passing to a tiny lipoma at L5/S1.
10. M.T.	6	Female	—	—	L2/3	+	+	—	The "thickened filum" was a lipoma extending from the conus to S1.
11. E.T.	3	Female	—	Expanded at the lower end with a small split.	L3	—	+	—	The bulbous and divided conus were confirmed. Only blood vessels passed through the split.
12. A.T.	28	Female	—	Small split	L3	+	+	—	A small spur was present, but only fibrovascular structures passed through the cord.
13. G.M.	11	Male	—	—	L4	+	+	—	
14. S.P.	13	Female	—	Restricted mobility	L2/3	+	+	—	

TABLE II

Correlation of myelographic and operative findings (*continued*)

Patient	Age	Sex	Scoliosis	Myelographic findings: Cord inc. mobility	Level of conus	Thickened filum terminal	Tethering bands	Mass	Comments The operative findings confirm the myelographic findings unless otherwise stated.
15. D.W.	6	Male	–	Expanded at lower end	L3/4	+ especially at lower end	+	–	The filum was infiltrated with fatty tissue, presumed to be lipomatous.
16. S.B.		Male	–	Thickened on posterior aspect	L1/2	–	+	–	Cervical dysraphism. The nature of the thickening of the upper cervical cord was not determined.
17. K.C.	11	Female	±	–	L4	–	+	–	The thickest band consisted of striated skeletal muscle and was contractile. This was separate from the filum.
18. S.J.	5	Female	±	Split eccentrically	L4	–	–	–	The left component of the split cord was atrophic. No evidence of a spur was found.
19. D.T.	14	Female	+	Atrophy Small split	L2	–	–	–	The cord was not split.
20. K.St.	8	Female	+	–	L3	–	+	–	
21. C.P.	14	Female	+	On concave aspect of bony canal	L3/4	–	+	–	
22. S.T.	22	Female	+	Split cord on concave aspect of bony canal	L3	+	+	–	Diastematomyelia with bony spur.
23. N.A.	5	Male	–	–	L3	–	–	–	Very expanded subarachnoid space below L3. Not considered to be surgically remediable.
24. C.F.	7	Female	–	Restricted mobility	L3	–	+	–	Parents declined operation.
25 K.Sh.	9	Female	–	–	L1	+	–	–	NO SIGNIFICANT ABNORMALITY The cauda equina lay in bundles with fine adhesions.
26. R.Phi.	13	Male	–	–	L2	–	–	–	Normal findings confirmed at operation.
27. S.O.	11	Male	–	–	L1	–	–	–	Normal findings confirmed at operation.

of the theca at this level is not uncommonly seen in normal patients, and this is usually attributed to epidural fat. Liliequist (1965) reports a single case of diastematomyelia investigated by gas myelography and describes, in addition to the splitting of the cord, the continuation of the conus as a narrow band and the presence of a soft-tissue mass in the subarachnoid space. He considers gas myelography to be the method of choice in the investigation of this type of patient and the findings closely resemble those of many of the patients in the present series. No mention is made of operative confirmation.

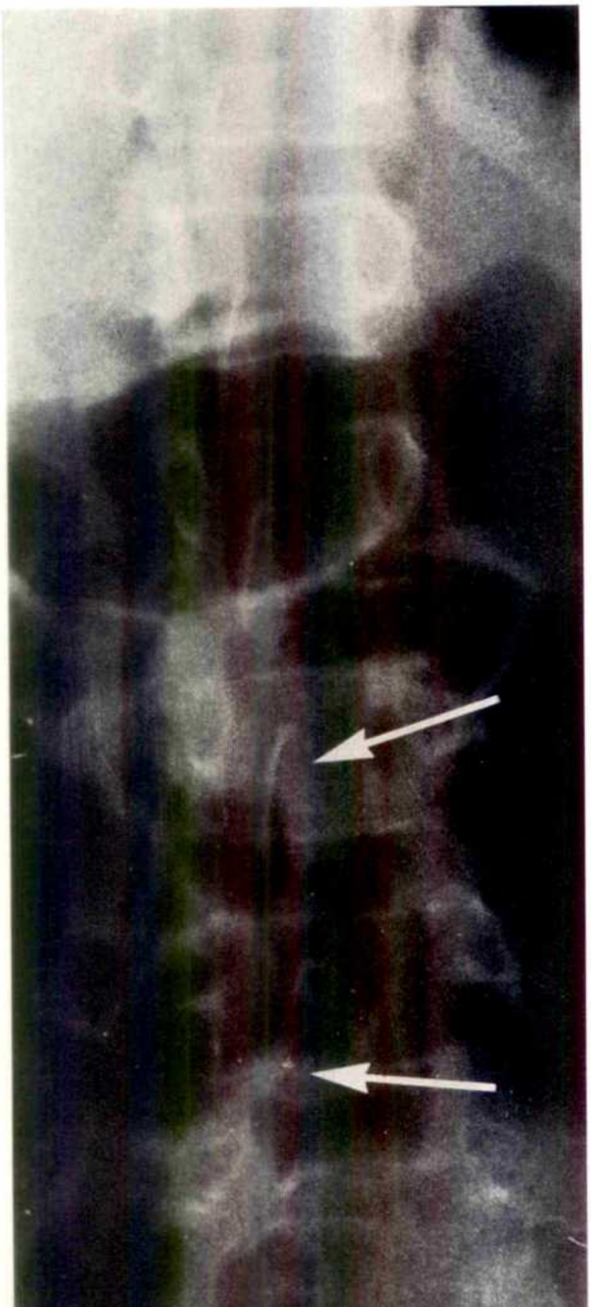

Fig. 12. *Case* 25 *K.S.h.*

Antero-posterior view of lumbar gas myelogram. The cord tapers at the level of LV1 and was thought to end here, but a long thickened and gradually tapering extension passes to LV5 (arrows). At operation the cauda equipa was bound into loose bundles by fine arachnoid adhesions but no significant abnormality was found.

Burrows (1968) illustrates an air myelogram showing a long tapering conus extending into the sacral canal and lying posteriorly. He suggests that air or gas myelography may become the technique of choice.

Gryspeerdt (1963) describes a high degree of accuracy in the diagnosis of a low termination of the conus, either directly when examining in the supine position or indirectly through the visualization of the anterior spinal artery when examining in the prone position. He mentions, however, that the contrast medium sometimes separates into droplets thereby making identification of these structures difficult. James and Lassman (1972) commenting on the same series of patients mention that when the conus is at a normal level it is "often very difficult to demarcate". Yashon and Beatty (1966) were unable to define the level of the conus by identifying the anterior spinal artery at positive contrast myelography. The technique of emulsification described by Bleasel (1961) overcame the difficulties of globulation of the contrast medium and demonstrated the cauda equina and conus but was associated with an unacceptable number of cases of adhesive arachnoiditis. Gold *et al.* (1969) consider that the technique of oil myelography is made more reliable by the use of much larger volumes of contrast medium. They describe seven dysraphic patients in whom up to 60 ml. of contrast medium were used in order to fill the lumbosacral sac completely. By this means the abnormal conus was delineated, but the contrast medium has to be removed at the end of the procedure and this, therefore, requires lumbar rather than cisternal injection. Even so, in spite of their cases generally showing more gross evidence of dysraphism than those in the present series, the myelograms failed to outline intradural lipomas in two of the seven patients. They comment that an air myelogram also failed to show the lesion in one of these patients. It seems likely that the density of such large volumes of contrast medium obscures small intradural lesions and furthermore, it is not possible to determine the freedom of movement of the conus in the way described above, even using large volumes, because of the difficulties caused by layering. Heinz *et al.* (1966) attempted to improve the technique by using less concentrated contrast media through which small lesions could still be defined. The number of patients examined was small, and the experimental contrast media that were used have not been marketed. Apart from these difficulties and disadvantages we feel that the introduction of an oily contrast medium, even for a short time, into the subarachnoid space, is undesirable in small children because of the possibility that adhesive arachnoiditis might aggravate the tension already existing upon the conus and cauda equina. Thus James and Lassman (1972) note a reaction to oily contrast medium (Myodil) in two out of 24 cases examined via the lumbar route and four out of 76 cases injected cisternally. This occurred in spite of very small amounts being used; between 2 ml. and 3·5 ml. at three years and 15 years of age respectively. There are many reports of arachnoiditis occurring after oil myelography (Peacher and Robertson, 1945; Tarlov, 1945; Luce *et al.*, 1951). There is an increased likelihood of arachnoiditis if there is some associated bleeding into the subarachnoid space (Howland and Curry, 1966). This particular group of patients might be particularly subject to traumatic lumbar puncture if performed for the purpose of aspiration of oil contrast. The existence of such adhesions would make surgery more difficult and interpretation of any subsequent myelogram would also be more difficult. Two normal patients in the present series have been re-examined by gas myelography. In both the initial normal features were again shown. It seems likely, however, that a water-soluble contrast medium suitable for examination of the entire spinal cord would possess all the advantages of gas, perhaps with enhanced definition.

At gas myelography, the spinal cord throughout its length, and more specifically the conus medullaris has been visible in every patient in the series, whether normal or abnormal, and in spite of the presence of severe scoliosis in four patients. In no case did the level of the conus as defined at myelography differ by as much as one segment from that recorded at operation. Surgical assessment of the level of the conus, is, of course, often unnecessary and sometimes not possible (James and Lassman, 1972). Thickened extensions of the conus, regarded as abnormalities of the filum terminale, have been defined in ten patients. The thickness of the normal filum has been taken as less than 2 mm with a thickness of 3 mm being regarded as definitely abnormal. The normal filum is not invariably seen. It is sometimes difficult to decide just at which point the true conus ends and the thickened filum terminale begins. This is not surprising as there is frequently a similar difficulty, at the subsequent operation, in determining the level to which functioning nervous tissue extends. Likewise, it has not been possible to suggest the pathological nature of such thickened extensions on the basis of the myelographic appearance. Again, a similar difficulty may be experienced at operation where densely adherent components of the cauda equina are often found in bundles around the filum. In the single misdiagnosed patient similar bundles were found, but were in no way densely attached either to each other or to the filum. When the thickened extension is associated with an expansion of the conus itself, it seems likely that an intramedullary lipoma is present with extension into the filum. This combination of abnormalities was seen on two myelograms in the series, both due to this cause. An enlargement of the conus without an associated extension to the lumbosacral level was seen in two further patients one of whom showed a small split in the cord and the other an intramedullary lipoma. Additional enlargements at the caudal end of a thickened filum at the lumbosacral level were found to be of varied pathology; small lipomas, tangles of nerves and blood vessels or, in one patient, contractile striated skeletal muscle.

In several patients, in whom the conus passed to a very low level, the observation that the emerging nerve roots passed in an upward direction was made at operation as described by James and Lassman (1972). Swedberg (1963) investigating cases of meningomyelocele by gas myelography found that he was unable to identify the nerve roots, and we have not been able consistently to do so in our patients. Gryspeerdt (1963) does not describe this feature at oil myelography. In a single case examined by oil myelography Yashon and Beatty (1966) describe the lumbar-root pouches as passing in a cranial direction. They were unable to discern this feature in two further patients with extremely low terminations of the cord. We have not found the root pouches to be visible on the gas myelograms. Tethering bands were identified in 15 patients, and apart from the association with low termination and fixation of the cord, these can usually be distinguished from nerve roots by their course, thickness and shape.

Varying degrees of splitting of the cord were suggested myelographically in five patients. Only one of these was of major degree, amounting to a lumbar diplomyelia with the two dural tubes separated by a bony spur. One further case showed the cord transfixed by a bony spur although in fact the split in the cord was small. In two further patients the cord was transfixed only by fibrovascular structures, although in one of these a small spur was present in addition. In the fifth patient no splitting of the cord was found at operation and the myelographic appearances are probably attributable to superimposed bowel shadow. This patient had severe scoliosis, and any form of myelography posed considerable technical problems. In another patient a small split in the cord was found at operation which had not been seen myelographically. In this patient there was no spur of any sort passing through the cord. Although no comparative investigations were made it might seem therefore that gas myelography, having produced one false-positive and one false-negative result in only six cases, is less reliable than oil myelography in the detection of this particular abnormality. It must be realized, however, that the splits being considered with the exception of the diplomyelia were very small; no more than 1–2 cm in length and with only slight separation of the two components.

After the examination is completed, the gas is absorbed rapidly. The morbidity of the procedure is surprisingly small, even among young children whose activity is difficult to restrict. Inevitably there is headache and some nausea. For some reason, however, these have been noticeably less severe than following pneumoencephalography. This could be because there is less extradural leakage of CSF following cisternal puncture than lumbar puncture. A few patients have complained of transient tinglings in the lower limbs. Oden (1953) suggested that warmed, humidified gas reduces the after effects of gas myelography, but he was not performing the investigation under general anaesthesia. The gas used for our patients has not been humidified and has been at room temperature. Thibaut (1969) described the withdrawal of gas at the end of the examination and the reintroduction of the CSF that had been removed earlier. In his cases this was accomplished by simultaneous lumbar and cisternal puncture which would not be appropriate for the present type of case. Furthermore he concludes that antibiotic cover is advisable since in his hands there were two cases of bacterial meningitis following the use of this technique in 29 patients compared with five cases among 800 other patients undergoing pneumomyelography or pneumoencephalography. It did not seem, therefore, that the limited morbidity justified any such modification of technique.

Conclusions

In this series of patients there is an extremely close correlation between the abnormalities shown at gas myelography and those found subsequently at operation. This confirms that at present this technique should be chosen for the pre-operative radiological assessment of patients suspected of occult spinal dysraphism.

Acknowledgments

I should like to express my thanks to my clinical colleagues, notably Mr. John Garfield and Mr. John Atwell for referring the patients for investigation and for never failing to provide me with clinical and operative details. I am indebted to the radiographic staff at the Wessex Neurological Centre, notably the Superintendent Radiographer, Miss Pamela Kimber, for the uniformly high technical quality of examination when this is of paramount importance and to the Teaching Media Centre, University of Southampton, notably Miss Susan Thyer for the illustrations and line-drawings; finally to Miss Sara Ryder for her patience and forbearance in typing the manuscript.

REFERENCES

Barson, A. J., 1970. The vertebral level of termination of the spinal cord during normal and abnormal development. *Journal of Anatomy*, *106*, 489–497.

Bleasel, K., 1961. Nerve root radiography. *British Journal of Radiology*, *34*, 596–601.

Burrows, F. G. O., 1968. Some aspects of occult spinal dysraphism. *British Journal of Radiology*, *41*, 496–507.

Cook, P. L., 1976. Clinical and radiographic findings in occult spinal dysraphism (*in preparation*).

Gold, L. H. A., Kieffer, S. A., and Peterson, H. O., 1969. Lipomatous invasion of the spinal cord associated with spinal dysraphism: myelographic evolution. *American Journal of Roentgenology*, *107*, 479–485.

Grant, D. N., 1972. Spinal dysraphism. *Postgraduate Medical Journal*, *48*, 493–495.

Gryspeerdt, G. L., 1963. Myelographic assessment of occult forms of spinal dysraphism. *Acta Radiologica Diagnosis*, *1*, 702–717.

Heinz, E. R., Brinker, R. A., and Taveras, J. M., 1966. Advantages of a less dense Pantopaque contrast medium for myelography. *Acta Radiologica Diagnosis*, *5*, 1024–1031.

Howland, W. J., and Curry, J. L., 1966. Pantopaque arachnoiditis. *Acta Radiologica Diagnosis*, *5*, 1032–1041.

James, C. C. M., and Lassman, L. P., 1972. In: *Spinal Dysraphism*, pp. 34–35 (Butterworths, London).

Jirout, J., 1966. Mobility of the spinal cord under abnormal conditions. *Acta Radiologica Diagnosis*, *5*, 1042–1046.

1969. In: *Pneumomyelography* (Charles C. Thomas, Springfield, Illinois).

Jones, P. H., and Love, J. G., 1956. Tight filum terminale. *Archives of Surgery*, *73*, 556–565.

Lichtenstein, B. W., 1940. Spinal dysraphism. *Archives of Neurology and Psychiatry*, *44*, 792–809.

Liliequist, B., 1965. Diastematomyelia. Report of a case examined by gas myelography. *Acta Radiologica Diagnosis*, *3*, 497–502.

Lombard, G., and Passerini, A., 1964. *Spinal cord diseases. A radiologic and myelographic review p.6* (Williams and Wilkins, Baltimore).

Love, J. G., Daly, D. D., and Harris, L. E., 1961. Tight filum terminale. Report of condition in three siblings. *Journal of the American Medical Association*, *176*, 31–33.

Luce, J. C., Leith, W., and Burrage, W. S., 1951. Pantopaque meningitis due to hypersensitivity. *Radiology*, *57*, 878–881.

Oden, S., 1953. Diagnosis of spinal tumours by means of gas myelography. *Acta Radiologica*, *40*, 301–313.

Peacher, W. G., and Robertson, R. C. L., 1945. Pantopaque myelography: Results, comparison of contrast media and spinal fluid reaction. *Journal of Neurosurgery*, *2*, 220–231.

Roth, M., 1969. Models of vertebro-neural relations. *Acta Radiologica Diagnosis*, *9*, 746–753.

Swedberg, M., 1963. Meningo- and myelomeningocele studied by gas myelography. *Acta Radiologica Diagnosis*, *1*, 796–805.

Tarlov, I. M., 1945. Pantopaque meningitis disclosed at operation. *Journal of the American Medical Association*, *129*, 1014–1016.

Thibaut, A., 1969. Myélographie gazeuse sélective totale. *Acta Radiologica Diagnosis*, *9*, 754–758.

Till, K., 1968. Spinal dysraphism: a study of congenital malformations of the back. *Developmental Medicine and Child Neurology*, *10*, 470–477.

Valentino, V., 1965. *Myelography* (Charles C. Thomas, Springfield, Illinois).

Yashon, D., and Beatty, R. A., 1966. Tethering of the conus medullaris within the sacrum. *Journal of Neurology, Neurosurgery* and *Psychiatry*, *29*, 244–250.

Book review

La phlébographie des membres inférieurs et supérieurs. By J. D. Picard, pp. 112, 1975 (Expansion Scientifique Française). 92.20F.

This monograph on phlebography of the lower and upper limbs by the distinguished French vascular radiologist, Professor J. D. Picard, makes a welcome appearance. It provides a useful companion monograph for two others with which the author is associated, *La lymphographie. Etude radiologique et clinique des voies lymphatiques normales et pathologiques* (1963) and *Arteriographie du membre supérieur et de la main* (1969).

La phlebographie is essentially a somewhat expanded radiographic atlas, and for this reason it is particularly gratifying to see the excellent standard of illustrations of the phlebograms. Unfortunately, comparison with the British equivalent shows how far behind we are in this aspect of our publications.

The book starts off with a description of the anatomy and physiology of the veins of the lower limb. These sections are illustrated with clear line diagrams, indicating the usual pattern, normal variations and the haemodynamics.

There follows a description of the author's technique for ascending phlebography. Unlike the reviewer, the author uses an overcouch technique with a long cassette. Such a technique is more likely to give rise to artefactual appearances than a fluoroscopic method, even though a short series of films is recommended. The patient is examined supine, with the use of tourniquets to direct the blood into the deep venous system. Professor Picard injects into a foot vein in a downstream direction, which on the whole produces less good filling of the deep venous system than injecting upstream, that is towards the toes. Despite this, the radiographs illustrated show adequate demonstration of the deep veins. For descending phlebography, the patient is examined, again with an overcouch tube, standing, and the contrast injected into either the popliteal or the femoral veins. This method is useful in demonstrating the competence or otherwise, of the valves of the deep venous system, but similar information can be obtained more comfortably with the patient in a semi-vertical position and the use of the Valsalva manoeuvre to project the contrast distally.

The next section deals with the normal appearances shown at phlebography and draws attention to some artefacts which may cause confusion in interpretation. After this, the appearances of venous thrombosis at its various stages, from acute loose thrombus to total occlusion, are described. There follow a few illustrations of a direct injection of varicose veins, before and after surgery—a procedure not often performed in this country, except in venous malformations.

Some venous dysplasias including the Klippel-Trenaunay syndrome are illustrated.

There is a brief section on the place of phlebography in venous trauma, and in operations for venous obstruction, such as the saphenofemoral bypass.

The last section on the lower limb deals with displacements and occlusions due to pelvic tumours.

In the part devoted to the upper limb, the illustrations of the normal anatomy are excellent. The basic technique for phlebography recommended is direct injection through a cannula in the anticubital fossa. There follow examples of venous thrombosis and occlusions both spontaneous and secondary to tumours, trauma and radiation.

The monograph finishes with a list of the most important indications for phlebography in the author's view.

A small criticism is that there is no index or any references. This could present difficulties for radiologists who may well not know, for instance, what Palma's and Halsted's procedures are.

Although the book is elementary, so is the knowledge of many general radiologists. For this reason, the book can be recommended as a quick reference atlas for all radiologists who may be called upon to carry out phlebography.

Although the reviewer had his copy professionally translated, the book can easily be used by anyone having a little French with the help of the clear figures.

M. Lea Thomas

1976, *British Journal of Radiology*, *49*, 516–518

Xerotomography of pulmonary lesions

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(*Received August, 1975 and in revised form January, 1976*)

ABSTRACT

Xerography in combination with tomography is a useful modality in evaluating pulmonary lesions. Comparison is made between this technique and conventional film tomography. Xerotomography is felt to be preferable although it requires considerably higher radiation exposure to the patient.

Xeroradiography has achieved wide acceptance in examinations of soft tissues, especially the breast. The ease with which masses can be visualized and calcifications demonstrated on xeromammograms prompted us to utilize this modality in evaluation of pulmonary lesions.

Four physical features make this process an excellent imaging medium for pulmonary lesions. First, the wide recording latitude permits visualization on the same image of structures varying in density from the relatively opaque mediastinum to the lucent periphery of the lungs (Chuang *et al.*, 1974; Wolfe, 1973) (Fig. 1). This obviates the need for specially designed filters required to demonstrate these structures on film tomograms. Oblique views also can be obtained without additional filters.

Secondly, wide exposure latitude permits establishment of relatively fixed techniques which are suitable for patients of varying sizes (Wolfe, 1969).

Thirdly, accentuation of interfaces between different densities (edge enhancement) aids in perception of borders of masses (Bedrossian and Martin, 1973) (Fig. 2).

Fourthly, selective reduction of low spatial frequency information, as found in off-fulcrum

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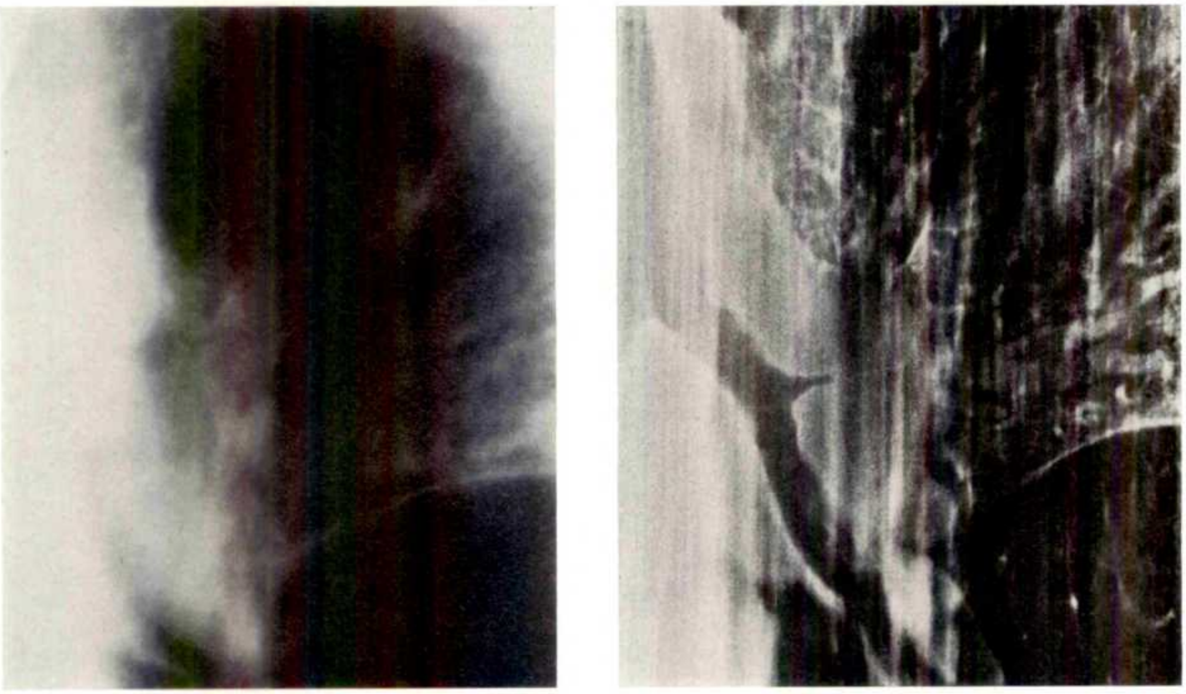
A
B

FIG. 1.

(A) Conventional film tomogram of mass in left hilar region which is surgically proven oat-cell carcinoma.
(B) Xerotomogram at the same level. Note better demonstration of trachea, main bronchi, and periphery of lungs. Bronchial occlusion by neoplasm clearly visible.

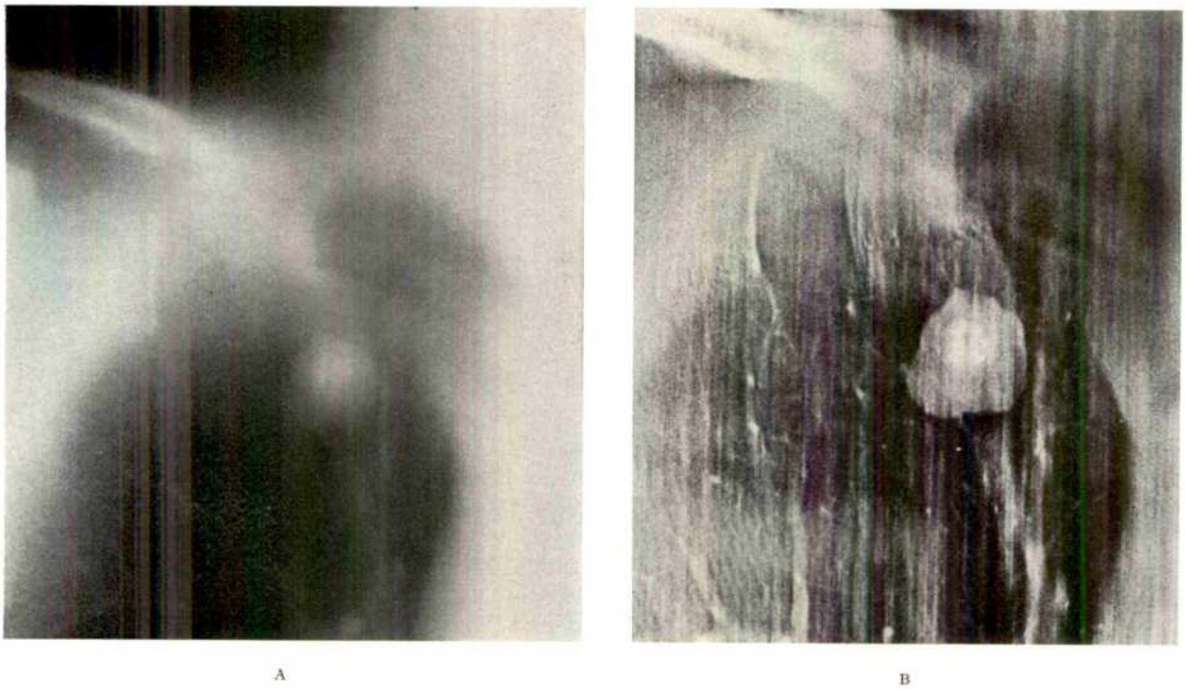

FIG. 2.

(A) Conventional film tomogram of granuloma with central calcification.
(B) Note the better delineation of the calcifications and borders of the mass on the xerotomogram.

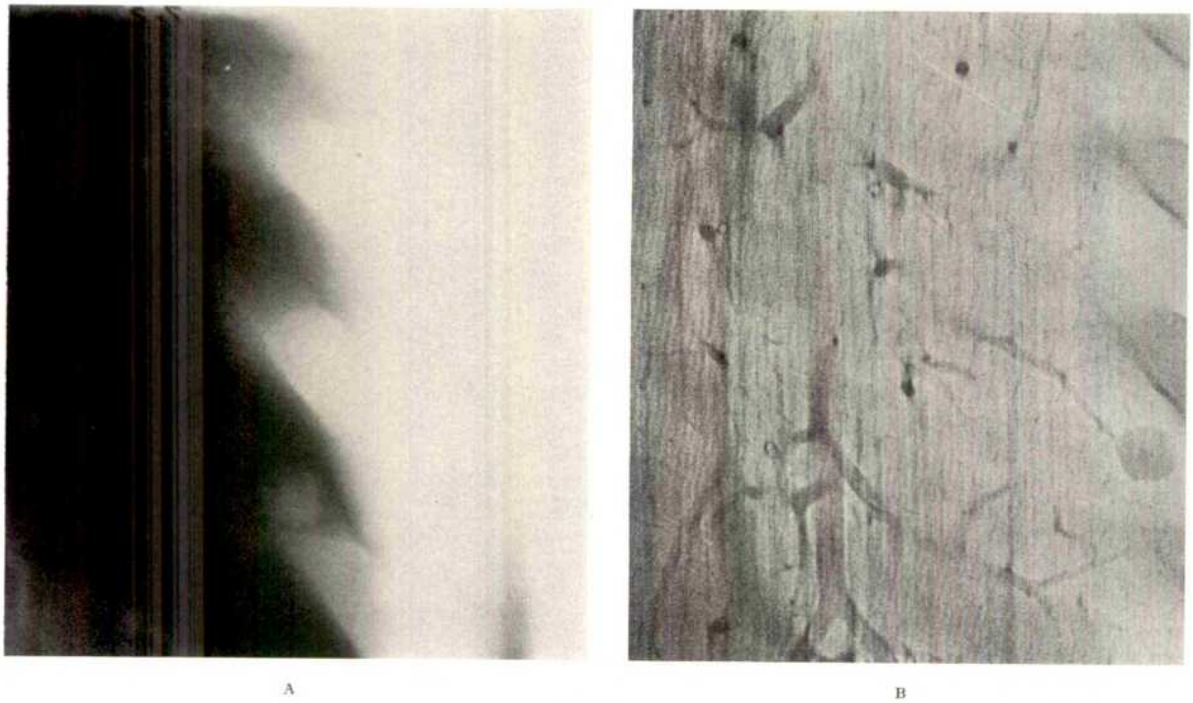

FIG. 3.

(A) Conventional film tomogram of hamartoma in the periphery of lung.
(B) Xerotomogram processed in the positive mode demonstrating margins of nodule and central calcification more distinctly.

planes, results in more distinct tomographic images (Harle *et al.*, 1975).

More than 50 patients with various pulmonary diseases were examined utilizing both conventional film tomography and xerotomography. Initially, film tomograms were obtained. Subsequently, a single xerotomogram was obtained at the level at which the lesion was best demonstrated. These studies were evaluated and compared in the 25 patients in whom there was pathological proof of disease. The edges of masses and borders of cavities were better defined on xerotomography in five patients. In no case were these features better visualized on conventional film tomograms. Calcifications were demonstrated with equal frequency on both recording media. Processing of the xerographic image in the negative mode (air appears dark as on radiographs) is appropriate for central lesions where the trachea and bronchi are to be visualized. Often peripheral nodules are demonstrated more clearly with positive processing (Fig. 3).

DISCUSSION

Xerotomographic images to us are preferable to film tomograms for the following reasons. Visually, the images are more pleasing to the eye. Margins of masses appear sharper. Calcifications are more distinct, although, in no case were calcifications seen on xerographic images when they were not visualized on film tomograms. The greatest advantage of xerotomographic imaging is in the evaluation of central pulmonary lesions. As mentioned previously, the ability to evaluate structures varying from the dense mediastinum to the radiolucent periphery of the lungs on one image eliminates the necessity of obtaining multiple films at various techniques and projections, and the need for additional filters.

The major objection currently to the routine use of xerotomography is that the amount of radiation exposure is about 15 times that required for conventional film tomography (Harle *et al.*, 1975). The quality of images and amount of information obtainable, however, leads one to utilize this recording modality when the lesion is centrally located and in patients in whom neoplasia is suspected. The detail present has made anticipated special studies such as bronchography unnecessary in several patients. Research is being carried out to increase the sensitivity of xerography and thereby reduce patient exposure.

SUMMARY

Xerography, coupled with tomography, is useful in evaluating pulmonary lesions. The physical features responsible are the wide recording and exposure latitude, edge enhancement, and suppression of off-fulcrum blur. Xerotomography yields the most fruitful results when demonstrating central lesions where both the mediastinum and less dense hilar regions are seen clearly on one image. Currently, the major obstacle to its routine use is the greater radiation exposure to the patient.

REFERENCES

BEDROSSIAN, C. W. M., and MARTIN, J. E., 1973. Xeroradiography of the lung. *Radiology*, *107*, 217–218.

CHUANG, V. P., DOUST, B. D., and TING, Y. M., 1974. Xerotomography of the mediastinum and tracheobronchial tree. *Radiology*, *111*, 457–477.

HARLE, T. S., HEVEZI, J. M., ROGERS, L. F., MARTIN, J. E., and JING, B. S., 1975. Xerotomography of the tracheobronchial tree. *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*, *124*, 353–357.

WOLFE, J. N., 1969. Xeroradiography of the bones, joints, and soft tissues. *Radiology*, *93*, 583–587.

WOLFE, J. N., 1973. Xeroradiography: Image content and comparison with film roentgenograms. *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*, *117*, 691–695.

Book review

Complications of Diagnostic Radiology. By J. F. Weigen and S. F. Thomas, pp. xiii + 557, 1973 (Illinois, U.S.A., Charles C. Thomas), $25.75.

In modern radiological practice the conscientious physician must always balance the hazards of not performing a necessary study against the potential dangers of the study. This book provides the essential facts on which to make such an assessment.

The first part of the book considers the physiological and pathological reaction to injections of organic iodides and other contrast media in great detail. This is followed by consideration of the complications of all the commonly performed specific examinations and prevention and treatment of the adverse reaction is discussed.

The book is written by general radiologists for general radiologists. None of the specialized studies are discussed by specialists in the particular field, but there is extensive reference to the literature which compensates for what some would consider to be a deficit. The book is very readable and what could be a dull subject is put in a way which stimulates interest. It is recommended both to radiologists and to those referring patients for radiological investigation.

B. KENDALL.

1976, *British Journal of Radiology*, *49*, 519–525

JUNE 1976

Differential diagnosis of chronic splenomegaly by grey-scale ultrasonography: Clinical observations and digital A-scan analysis*

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(*Submitted April, 1975 and in revised form November, 1975*)

ABSTRACT

Hitherto, ultrasound examination of the spleen has been limited to the determination of size and position. Grey-scale ultrasonography involves enhanced signal-to-noise ratio so that the soft-tissue texture is displayed, and this permits the recognition of diffusely abnormal consistency. This facility was used to predict lymphomatous involvement of the spleen in patients coming to laparotomy in whom an accuracy of 77·8 per cent was achieved.

Three types of splenic consistency are described in a series of 60 patients presenting with chronic splenomegaly: Very low-level echoes emanate from malignantly involved spleens. Medium-level echoes are found in various benign conditions and high-level echoes occur in various chronic inflammatory conditions. These differences were confirmed and quantitated by computerized A-scan analysis.

Grey-scale imaging techniques produce quantitative information on the amplitude of the echoes emanating from the internal structure of an organ. This can be used in the differential diagnosis of hepatic or splenic pathology. The techniques used by Kossoff (1974) for grey-scale visualization have been applied to the imaging of fine detail within the liver (Taylor *et al.*, 1973). In general it may be stated that neoplastic replacement of liver tissue results in areas returning lower level echoes than normal while any chronic inflammatory state results in increased echo amplitude. For example, high-level echoes have been noted in fibrotic replacement of tumour following radiotherapy (Taylor, 1974) and following chemotherapy (Gilby and Taylor, 1975). Cirrhosis of the liver also results in abnormally high level echoes (Holmes, 1966). Fields and Dunn (1973) produced theoretical evidence which rationalized and substantiated these empirical observations. They pointed out that it is difficult to account for the magnitude of the returned echoes from soft tissues purely in terms of the relatively small differences in acoustic impedances between them and derived an expression in which the magnitude of the echo amplitude was expressed in terms of the difference in bulk moduli of the media at an interface In particular, they noted that the supporting elements, such as collagen and elastin, have bulk moduli which exceed those of other tissues by several orders of magnitude. With this rationalization, grey-scale visualization of soft organs must be considered as the display of the fibrous skeleton which is replaced by malignancy and increased in fibrotic and cirrhotic states.

Mountford and Wells (1972a; 1972b) analysed A-scans emanating from the livers of normal and cirrhotic subjects and reported that there were significantly higher echo amplitudes in cirrhotic livers than in the normal. However, in the present clinical situation, the differential diagnosis of hepatobiliary disease by grey-scale ultrasound is more dependent upon pattern recognition than merely on data concerning echo amplitude. Thus, although computers are capable of, and suited to, rapid A-scan analysis most diagnostic potential lies in the spatial distribution of the echo amplitude; such pattern recognition is largely beyond current computer technology but presents no problems to the trained diagnostician. However, there remain two further applications for such computer analysis: to aid in the differential diagnosis of splenomegaly, and in the mass screening of populations exposed to vinyl chloride to detect early periportal fibrosis.

CLINICAL OBSERVATIONS

In a series of 60 patients referred for ultrasound examination of the spleen, it was noted that different pathologies tended to be associated with different echo amplitudes from the spleen substance. Clinical experience showed that this was of value in the differential diagnosis of splenomegaly, assuming that the increased echo amplitude was due to increased fibrous content resulting from an inflammatory process.

Methods

The equipment used in these studies was custom built and produced high quality grey-scale images

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*Part of MD Thesis, K. J. W. Taylor, University of London.

TABLE I

DIAGNOSES OF PATIENTS WITH CHRONIC SPLENOMEGALY

Low-level echoes (N.B. all malignant)	
Hodgkin's disease and lymphomas	20
Leukaemias	10
	30
Medium-level echoes	
Cirrhosis and portal hypertension	15
Myelofibrosis	3
Polycythaemia rubra vera and DXT	2
Non-tropical hepato-splenomegaly	1
	21
High-level echoes	
Sarcoidosis	2
Brucellosis	2
Tuberculosis	1
Malaria	1
Lymphoma (spleen not involved in one)	2
Myeloproliferative disorder	1
	9
Total	60

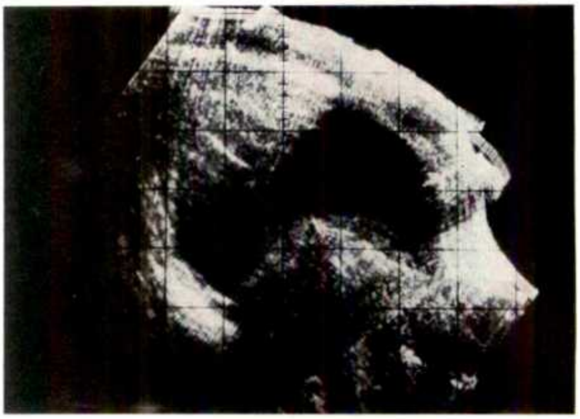


FIG. 1.

Oblique B-mode ultrasonogram of spleen showing normal consistency.

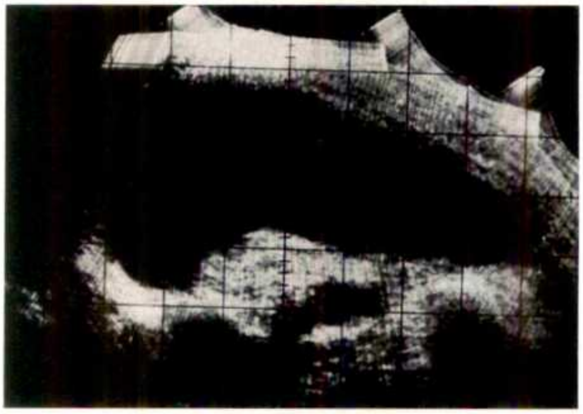


FIG. 2.

Oblique B-mode ultrasonogram of spleen showing marked enlargement and virtually echo-free consistency. This is characteristic of a leukaemic spleen.

(Hill and Carpenter, 1976). Ultrasonic examination of the spleen usually followed examination of the liver since this frequently assisted in the differential diagnosis of hepatomegaly. Compounded scans were usually carried out since the degradation of resolution inherent in compounding was unimportant when recording the echo amplitude (Taylor and Hill, 1975). The method of scanning varied with the spleen size: a relatively small spleen was scanned obliquely along the 10th intercostal space with the patient lying in the right lateral position. Larger organs could be scanned in either the transverse or longitudinal plane and the spleen size could be estimated by measuring the longitudinal axis deep to the 10th intercostal space. The amplitude of the returned echoes could be qualitatively estimated on the A-scan appearance of a beam through the spleen substance and this was apparent in the brightness of the B-mode display.

Results

The clinical diagnoses and the number of patients in each category are given in Table I. The normal splenic consistency is shown in Fig. 1, while a leukaemic spleen is shown in Fig. 2. The spleen is not only enlarged but appears, if anything, a little blacker than the normal consistency. This difference is, however, best judged by examination of the A-scan at the time of examination. Involvement of the spleen by Hodgkin's disease or lymphoma results in varying degrees of splenomegaly and a slight decrease in echo amplitude. These criteria were used to predict the possibility of splenic involvement in 20 patients coming to a staging laparotomy for lymphoma or Hodgkin's disease. The accuracy of this prediction is shown in Table II. Energetic treatment of leukaemias may slightly increase the echo amplitude producing fine structure in the spleen substance but to a lesser extent than in the conditions described below.

Intermediate level echoes are seen in a number of relatively benign conditions including myelofibrosis, splenomegaly secondary to portal hypertension, non-tropical hepato-splenomegaly (Fig. 3) and polycythaemia rubra vera after irradiation.

TABLE II

ACCURACY OF ULTRASOUND PREDICTION OF SPLENIC INVOLVEMENT IN 20 PATIENTS WITH HODGKIN'S DISEASE AND LYMPHOMAS UNDERGOING LAPAROTOMY*

Correctly + ve	7/9 = 77·8
Correctly − ve	8/11 = 72·7
False + ve	3/11 = 27·3
False − ve	2/9 = 22·2

*From Glees *et al.*, 1975.

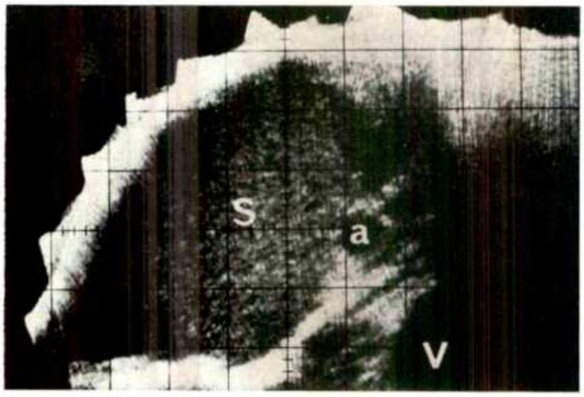


FIG. 3.

Transverse B-mode ultrasonogram of spleen (S) which is markedly enlarged and fills the left half of the abdomen. A fine pattern is seen throughout the organ substance, similar to that seen in the placenta. This is consistent with benign non-tropical hepato-splenomegaly. V is the body of the first lumbar vertebra. A large splenic artery (a) is well visualized.

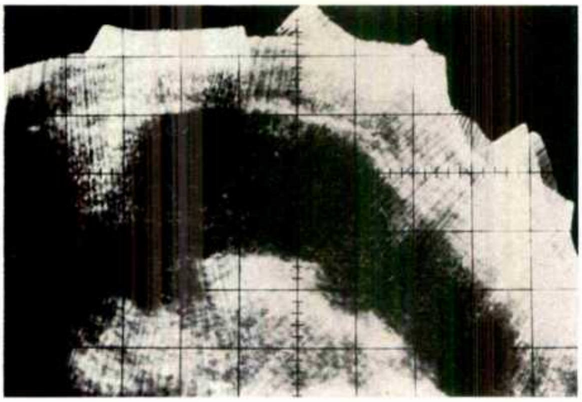


FIG. 4.

Oblique B-mode ultrasonogram of spleen which is markedly enlarged and returns medium level echoes which are displayed as a fine structure throughout the organ. This appearance is consistent with splenomegaly due to portal hypertension.

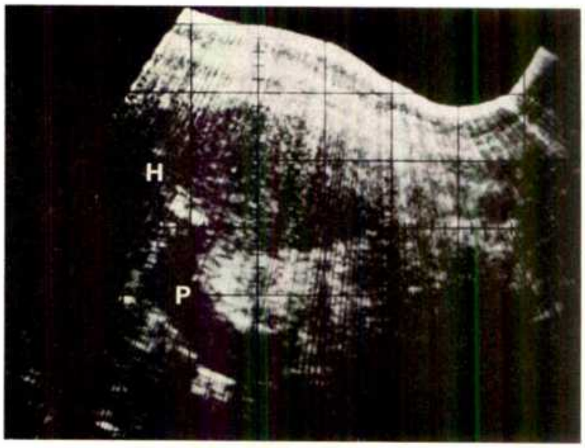


FIG. 5.

B-mode ultrasonogram of porta hepatis (parasagittal section) showing gross enlargement of the portal vein (P) ascending into the liver (H). Such appearances indicate portal hypertension.

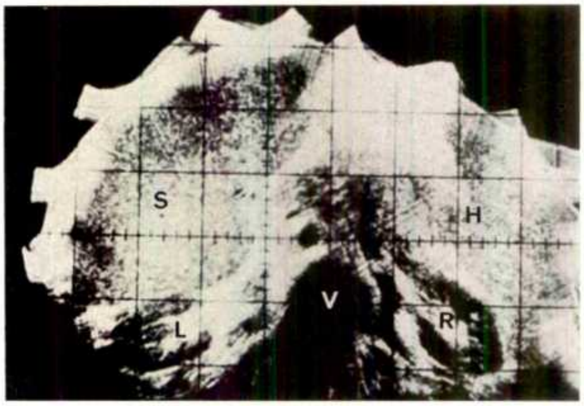


FIG. 6.

Axial B-mode ultrasonogram at the level of the first lumbar vertebra (V). Very high-level echoes originate from both the liver (H) and spleen (S). Such echoes from both organs indicate a chronic inflammatory process producing hepato-splenomegaly. This scan was from a patient with tuberculosis. The left (L) and right (R) kidneys are well shown.

Splenomegaly due to portal hypertension, most frequently due to cirrhosis, is particularly easy to diagnose by ultrasound since the liver returns abnormally high level echoes (Holmes, 1966), the spleen has a characteristic fine structure (Fig. 4) and the portal vein can be visualized at the porta hepatis and appears both large and tortuous (Fig. 5) in portal hypertension (Taylor and Carpenter, 1975).

The highest echo amplitudes from the spleen substance have been observed in chronic inflammatory causes of splenomegaly including malaria, tuberculosis, brucellosis and sarcoidosis. Figure 6 shows a transverse axial tomogram of a patient referred with a presumptive diagnosis of lymphoma. Ultrasonic examination of the liver and spleen revealed an even distribution of very high-level echoes throughout both organs. These appearances were reported as indicative of a chronic inflammatory process and strongly against a malignant one. The lymphogram and clinical findings supported the diagnosis of a lymphoma and a diagnostic laparotomy was carried out. The cut surface of the spleen showed white nodules throughout and similar lesions were present in the liver. However, the ultrasound findings were vindicated by the subsequent histological findings of tuberculosis.

Three patients in this group with malignancies are of special interest. In one of these, the spleen showed only benign enlargement at subsequent splenectomy: in the other lymphoma, the spleen was involved and no explanation can be given at present for the unusual appearance. The patient with a myelo-proliferative disorder was of great interest. Splenomegaly had been present for 18 years following a febrile illness in Singapore in childhood. The eventual diagnosis, after splenectomy, was a hyperimmune myeloproliferative disorder with renal amyloidosis. In many ways, therefore, the splenic consistency would be expected to simulate a chronic inflammatory process.

DIGITAL QUANTIZATION OF A-SCAN THROUGH THE SPLEEN SUBSTANCE

The above results were of considerable clinical value although they were based upon qualitative observations and highly dependent on the experience of the operator. Moreover, it is possible that similar changes in appearance could have been produced by variations in amplifier gain and absorption compensation settings. However, the findings have been supported by quantitative analysis using a small on-line computer; this has indicated how results which are less dependent on operator experience may be obtained.

Method

The ultrasound equipment was used as described above to produce a normal B-mode display through the spleen. The computer was then switched on-line and the scan repeated. During this process the signals from the scanner were digitized and stored in the computer (Digital Equipment Corporation: PDP 8/E, 12K words of memory, 1·6 M word magnetic disc).

In order to produce standardized data when the computer was on-line, a constant tissue-absorption correction was maintained, no attenuation was used and the echo signal range was compressed by means of a full-range logarithmic amplifier. The output from this was processed by means of a peak detector and 128 samples of each A-scan contributing to the B-mode display were digitized to a precision of 6 bits. The signals from the positional potentiometers were digitized separately to a precision of 12 bits and both sets of data stored on the magnetic disc in real time.

When the scan was complete, the data stored on the disc were processed to produce a B-mode display on a colour television display system. This display has a resolution of 96 × 96 points and uses the temperature scale (red-orange-yellow-white) to represent echo amplitude. An advantage of such a colour scheme is that half-tone photographs are meaningful. A facility was provided in the processing program to superimpose on the display a pair of crosswires (Fig. 7) which were positioned to delineate a particular area of interest. The data stored on the disc were then processed to extract quantitative information on all the echoes within the delineated area. The mean and standard deviation of echo size were calculated and a histogram produced of echo amplitude against frequency of occurrence.

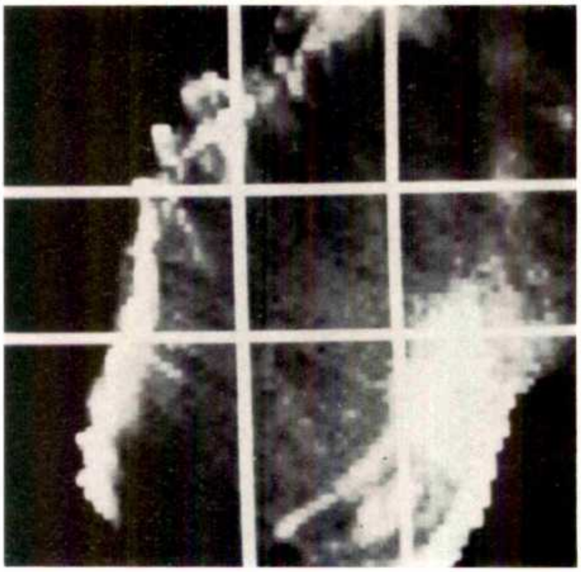
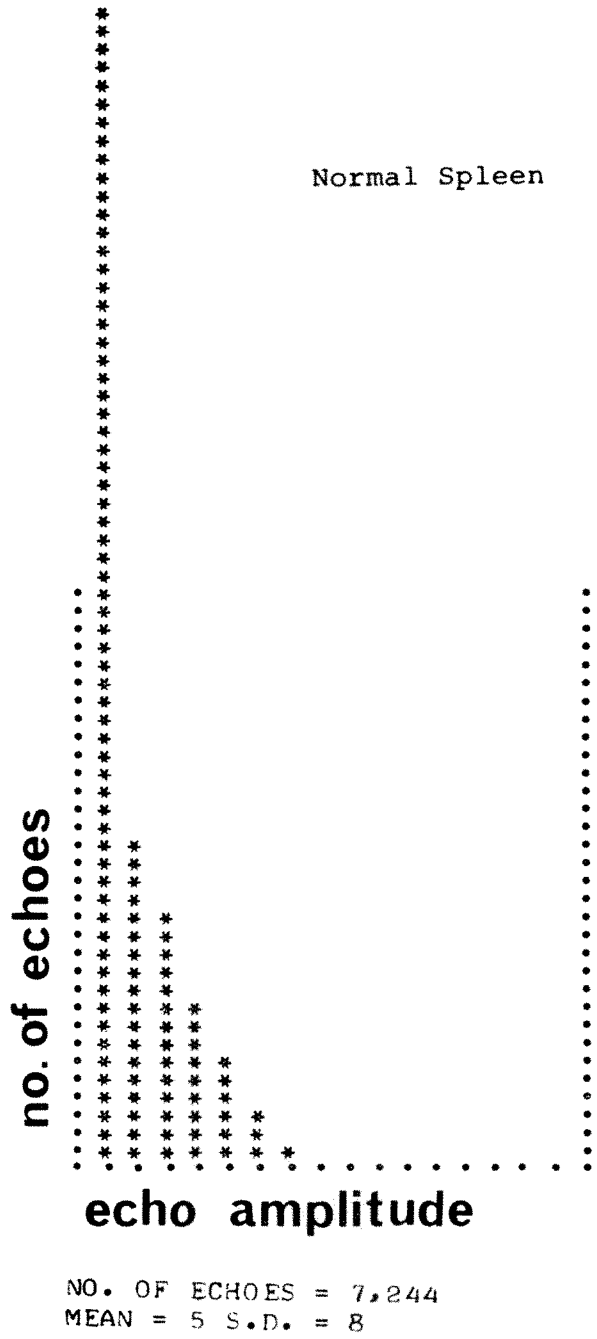
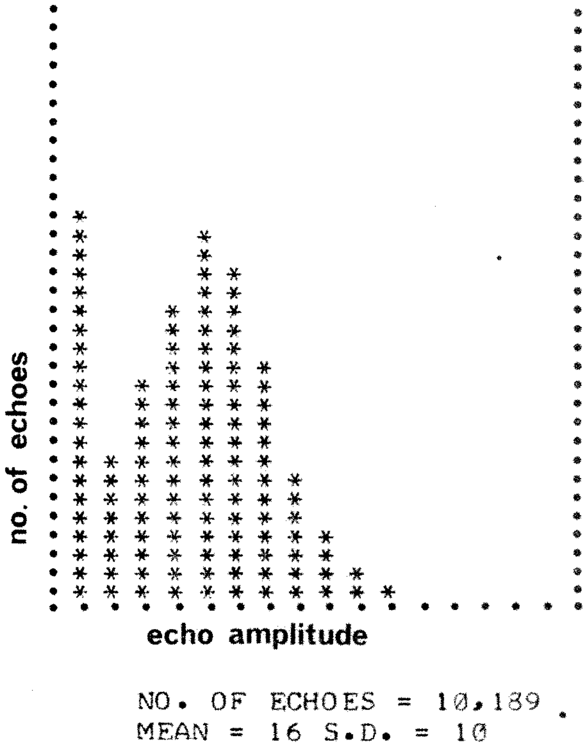


FIG. 7.

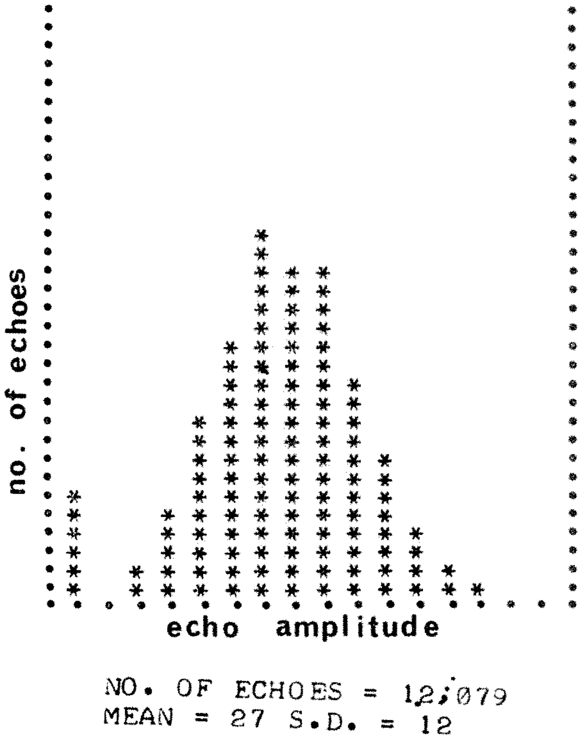
Computer-processed ultrasonogram of spleen with superimposed crosswires to delineate area of interest.



A



B



C

FIG. 8.

(A) Histogram of echo amplitudes from normal and neoplastic spleens.

(B) Histogram of echo amplitudes in cirrhosis, myelofibrosis, etc. listed in Table I.

(C) Histogram of echo amplitudes from spleens with high level echoes listed in Table I.

Results

The three categories of splenic consistency defined in Table I are illustrated in Fig. 8A–C. Figure 8A is the histogram of the normal splenic consistency and, with present technology, cannot be distinguished from malignant involvement. In conditions such as cirrhosis, myelofibrosis, etc., the spleen returned echoes of the size and distribution shown in Fig. 8B. The chronic inflammatory causes of splenomegaly listed in Table I produced histograms characterized by Fig. 8C. On first examination it appears that there is a loss of a Gaussian distribution with the appearance of two populations in the medium level echo range. However, further examination persuaded us that the large number of echoes appearing in the first bin was due to a summation of all the low echoes which constituted the lower tail of the Gaussian distribution. If this is true then the only difference between each histogram is the progressive shift towards the right and these results are intended only to illustrate a method in which quantitative information may be obtained on splenomegaly. Insufficient data have been obtained to define confidence limits for the mean echo amplitude of each of the three categories; also it is not possible to equate any category to its corresponding absolute mean echo amplitude as this depends on many factors such as transducer characteristics, amplifier gains, etc.

DISCUSSION

The spleen is a difficult organ to examine, being inaccessible to palpation unless moderately enlarged, whilst clinical evaluation of the consistency of an enlarged spleen is of limited value. Isotope imaging permits estimation of organ size but this has little relation to pathological involvement (Gazet, 1973) and does not contribute towards the differential diagnosis of splenomegaly.

Splenoportography may be highly informative but is also highly invasive while ultrasound promises to be more informative, and totally non-intrusive. In theory, any pathology which may be recognized by the pathologist or surgeon by examining the cut surface of the spleen should be apparent to the ultrasonologist on an ultrasound tomographic cut. In practice, some improvement is required in the signal-to-noise ratio before lymphomatous infiltration can be differentiated from the normal consistency with certainty. Ideally, the normal consistency should be displayed. In the patients described here, it is interesting to note that the ultrasound prediction of splenic involvement with lymphoma or Hodgkin's disease was correct in 77·8 per cent of involved spleens and 72·7 per cent of non-involved spleens. The fact that this difference was not apparent on digital analysis suggests either some degradation in the analog to digital converter or in the digital signal processing. In either case, technical improvements can be carried out.

To date, ultrasound scanning of the spleen has only been used to estimate volume (Kardel *et al.*, 1971). Indeed, conventional scanners do not have sufficient signal-to-noise ratio to display the consistency of the spleen, even in chronic inflammatory states. However, this series of patients suggests that valuable diagnostic data are available from the grey-scale method. In these patients with chronic splenomegaly, all 30 spleens returning very low-level echoes were malignant. In 30 spleens returning medium to high level echoes, 28 were benign (medium level echoes were only obtained in polycythaemia rubra vera after radiotherapy to the spleen). There are of course, many other causes of splenomegaly which we have not had the opportunity to examine so that these results are rather preliminary ones.

The findings reported here strongly support the concept proposed by Fields and Dunn (1973) and imply that grey-scale ultrasound visualization results largely in the display of the fibrous skeleton of soft tissues. Thus, chronic inflammatory disease results in increased echo amplitude while cellular infiltration returns very low-level echoes. It might be expected that nodular-sclerotic Hodgkin's disease would produce a similar appearance but to date this has not been found. One possible explanation for this is that echoes are produced but are locally attenuated by abnormal cell masses. This is in accordance with our observations on some patients with early Hodgkin's disease who present very low level echoes from the liver and who on biopsy, are found to have extensive periportal infiltration with lymphocytes. This we interpret as being due to local attenuation of echoes produced by a normal fibrous skeleton.

A-scan analysis was first reported by Mountford and Wells (1972a; 1972b) for the diagnosis of cirrhosis. Our attempts to apply the digitized technique to other liver diseases have been largely unsuccessful since the data on spatial distribution of echoes are lost. Thus, many diffuse diseases of the liver which produce a characteristic pattern do not produce significantly different histograms of echo amplitude. Further, there are wide variations in the norm but in the same subjects the results are repeatable over long periods of time. The technique could, therefore, be used to assess increasing pathology of the liver in patients prone to cirrhosis for social or other reasons.

Exposure to vinyl chloride has been causally related to development of liver haemangiosarcomata which is presumed to be preceded by fibrotic changes. The application of the technique described in this paper to the serial examination of the liver would permit the early signs of fibrosis to be detected when full grey-scale ultrasound examinations could be performed to visualize the portal vein and spleen. The addition of the computer facility permits repeated mass examinations of populations exposed to hepatotoxic agents by relatively unskilled technicians.

ACKNOWLEDGMENTS

We would like to thank Dr. McCready for the facilities of his department, and Dr. Hill for his helpful comments in the preparation of this paper.

REFERENCES

FIELDS, S., and DUNN, F., 1973. Correlation of echographic visualizability of tissue with biological composition and physiological state. *Journal Acoustical Society of America*, *54*, 809–812.

GAZET, J. C., 1973. Laparotomy and splenectomy. In *Hodgkin's Disease*, edited by Sir David Smithers, pp. 190–200 (Churchill-Livingstone, Edinburgh and London).

GILBY, E. D., and TAYLOR, K. J. W., 1975. Ultrasound monitoring of hepatic metastases during chemotherapy. *British Medical Journal*, *1*, 371–3.

GLEES, J., TAYLOR, K. J. W., GAZET, J. C., and PECKHAM, M. J., 1976. Accuracy of grey-scale ultrasonography of liver and spleen in Hodgkin's disease and other lymphomas compared with isotope scans. *Clinical Radiology* (in press).

HILL, C. R., and CARPENTER, D. A., 1976. Ultrasonic echo imaging of tissue: instrumentation. *British Journal of Radiology 49*, 238–243.

HOLMES, J. H., 1966. Ultrasonic diagnosis of liver disease. In *Diagnostic Ultrasound*, edited by C. C. Grossman, J. H. Holmes, C. Joyner and E. W. Purnell, pp. 249–265 (Plenum Press, New York).

KARDEL, T., HOLM, H. H., RASMUSSEN, S. N., and MORTENSEN, T., 1971. Ultrasonic determination of liver and spleen volume. *Scandinavian Journal Clinical and Laboratory Investigation*, *27*, 123–128.

KOSSOFF, G., 1974. Display techniques in ultrasound pulse echo investigations: A review. *Journal of Clinical Ultrasound*, *2*, 61–72.

MOUNTFORD, R. A., and WELLS, P. N. T., 1972a. Ultrasonic liver scanning: the quantitative analysis of the normal A-scan. *Physics in Medicine and Biology*, *17*, 14–25.

1972b. Ultrasonic liver scanning: the A-scan in the normal and in cirrhosis. *Physics in Medicine and Biology*, *17*, 261–269.

TAYLOR, K. J. W., 1974. Ultrasonic patterns of tumours of the liver. *Journal of Clinical Ultrasound*, *2*, 74–76.

TAYLOR, K. J. W., CARPENTER, D. A., and MCCREADY, V. R., 1973. Grey-scale echography in the diagnosis of intrahepatic disease. *Journal of Clinical Ultrasound*, *1*, 284–287.

TAYLOR, K. J. W., and CARPENTER, D. A., 1975. The anatomy and pathology of the porta hepatis demonstrated by grey-scale ultrasonography. *Journal of Clinical Ultrasound*, *3*, 117–121.

TAYLOR, K. J. W., and HILL, C. R., 1975. Scanning techniques in grey-scale ultrasonography. *British Journal of Radiology*, *48*, 918–920.

Book review

Radiopharmaceuticals. Edited by G. Subramanian, B.A. Rhodes, J. F. Cooper and V. J. Sodd, pp. 555, 1975 (New York, The Society of Nuclear Medicine, Inc.), $30.00.

This book is based on an International Symposium on Radiopharmaceuticals held in Atlanta, Georgia, in 1974. The idea of the symposium was to bring together a wide variety of people engaged in the production of radiopharmaceuticals in order to generate a comprehensive review of the developments, with up-to-date information on radiopharmaceutical technology. Most of the contributions came from the United States, but there were a few selected from overseas centres. Certainly the Conference was successful in its aim and the resultant publication is very comprehensive, covering most aspects of radiopharmaceuticals and the use of radioactive diagnostic agents in static and dynamic studies.

The book opens with a short section on basic concepts involved in the production and use of radioactive and diagnostic agents. This is followed by sections on the main isotopes in use today including ^{99}Tc^{m}, indium and the halogens. The section on technetium is valuable, covering aspects missing from most of the current texts, including chemistry of technetium, labelling of proteins, red blood cells and phosphonates.

The section on the use of halogens includes the production and use of ^{123}I. Other papers deal in general terms with the production and use of cyclotron generated isotopes. The use of radioactive nitrogen is covered briefly. Papers on quality control include analytical methods of chromatography, sterile kits, microbiology and legal problems. The last eight sections deal with the specific application of radiopharmaceuticals to lung studies, bone, heart, kidney, cisternography, tumour localization and the detecton of deep vein, thrombosis.

The non-homogeneous nature of the publications following many conferences makes one wonder if they are of more benefit to the publisher, rather than to the authors or purchasers of the finished books. One feels this book is an exception to the general rule, the finished volume giving a very useful review of the state of radiopharmaceutical developments at the present time. In general, the papers are of a good standard, bringing together a wealth of experience on the subject. It will be very valuable as a substitute for a formal text-book on radiopharmacology. However, it does emphasize the lack of such a text-book at the present time. The editors are to be congratulated on their careful choice of invited and proffered papers. It is hoped that the subject will be brought up to date from time to time, with perhaps less emphasis on the clinical aspects which can be found easily elsewhere in the multitude of publications now available on nuclear medicine.

V. R. MCCREADY.

1976, *British Journal of Radiology*, *49*, 526–532

Report on treatment of cancer of the ovary

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(*Received December, 1974 and in revised form November, 1975*)

ABSTRACT

A malignant ovarian tumour has been diagnosed in 373 patients referred to the R.R.T.I. from January 1966 to June 1972. Serous ovarian carcinoma was the commonest type and occurred in 254 patients. The results in these patients are studied in detail after staging according to F.I.G.O. recommendations. Following surgery and post-operative radiotherapy, chemotherapy was started immediately in all patients with progressive disease and after randomization also in 50 per cent of the others. The three-year survival rate in Stage II patients tended to be more favourable following irradiation of the pelvis and lumbo-aortic nodes (55 per cent) than following radiotherapy restricted to the pelvic area (40 per cent). The dose should be 5–6 krad. The five-year survival was 68 per cent for Stage I, 26 per cent for Stage II and nearly zero for Stages III and IV, as well as for patients referred for treatment of a recurrence. In spite of whole-abdomen irradiation 50 per cent of the patients in the latter three groups were deceased within eight months; therefore chemotherapy should be preferred. The main problem in ovarian cancer is late diagnosis. Evaluation of results is difficult because numerous variable factors concerning pathology and treatment make it necessary to sub-divide the patients into groups too small for statistically reliable conclusions. Each treatment factor should be studied by a group of hospitals.

MATERIAL AND METHODS

From January 1966 to June 1972, 373 patients were referred to the Rotterdamsch Radio-Therapeutisch Instituut (R.R.T.I.) with a diagnosis of malignant ovarian tumour. Grouping according to histological diagnosis is shown in Table I. This report will deal mainly with the most frequently occurring type: serous ovarian carcinoma. In these patients the results are studied in detail after staging according to F.I.G.O. recommendations (F.I.G.O. News, 1965): Table II. Treatment started with surgery performed by the referring gynaecologist and was supplemented by post-operative radiotherapy. This was immediately followed by chemotherapy in patients with progressive disease when irradiation had been completed and also in 50 per cent of the others selected by randomization. The criteria for progressive disease were: any sign of growing solid tumour or increasing effusion irrespective of site. Delayed chemotherapy was started when a relapse occurred during follow-up of patients without treatment subsequent to radiotherapy. Chemotherapy was applied by means of sequential administration of agents with different activity in distinct phases of mitosis: Cyclophosphamide (i.v. 200 mg/day, three weeks), interval two weeks, Vincaleucoblastin (i.v. 1×10 mg/week, four weeks), interval two weeks, 5 Fluoro-Uracil (i.v. 3×750 mg, first week, 1×750 mg second, third and fourth week), interval two weeks.*

Radiotherapy was applied by means of a 6 MV linear accelerator through anterior and posterior fields, with the patient supine. There was no shielding of kidneys, liver or spleen. Treatment was given five days per week. The dose to pelvis and lumbo-aortic nodes was 5 krad (4 krad in 1966 only) and to

TABLE I

PATIENTS REFERRED TO THE R.R.T.I. BECAUSE OF A MALIGNANT OVARIAN TUMOUR FROM JANUARY 1966 TO JUNE 1972.
(Grouping according to histological diagnosis)

Histological diagnosis	Number of patients	
Serous carcinoma		254
Mucinous carcinoma	22	
Endometrioid carcinoma	16	
Mesonephric carcinoma	21	
Undifferentiated carcinoma	13	
Dysgerminoma	10	
Malignant granulosacell tumour	22	
Malignant teratoma	2	
Dermoid cyst with malignant transformation	7	
Sarcoma	4	
Malignant thecoma	1	
Malignant sertolicell tumour	1	
		119
		373

TABLE II

STAGE DISTRIBUTION OF SEROUS OVARIAN CARCINOMA IN PATIENTS REFERRED TO THE R.R.T.I. FROM JANUARY 1966 TO JUNE 1972

Stage (F.I.G.O.)	Number of patients	%		
Ia	34	15·4		
Ib	10	4·5	23·1	
Ic	7	33·2		
II	67		30·3	100
III	76		34·4	
IV	27		12·2	
Recurrence	33			
Total	254			

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*Chemotherapists: W. F. Stenfert Kroese and J. Blonk vd Wÿst.

the upper abdomen 2·5 krad in 1966 but 2 krad in later years because of severe kidney damage in three patients. The corresponding daily doses were 150–200 rad and 75 rad respectively. A pelvic dose of 6 krad was given to 14 patients (six referred for recurrence, three Stage II and five Stage III). In ten patients radiotherapy had to be abandoned before a dose of 4 krad was reached. The positions of the fields are shown in Fig. 1.

RESULTS

The three-year survival rate is shown in relation to the *irradiated area* for Stages I, II and III and IV in Fig. 2. Enlargement of the treated area beyond the pelvis (lumbo-aortic and/or upper abdomen) may give better results in Stage II patients. Metastases in the lumbo-aortic nodes were demonstrated in 16 out of 50 post-mortem examinations. More detailed figures concerning Stage II patients treated with a dose of at least 5 krad to the pelvis reveal a trend to a better survival rate from 40 to 55 per cent in association with a dose of 5 krad administered to the lumbo-aortic region (Fig. 3). Inclusion of the lumbo-aortic nodes in the irradiated area might be useful. The three-year survival rate in relation to the *total dose to the pelvis* is shown with grouping according to stage in Fig. 4. A trend to better results in patients treated with a higher dose might be assumed for Stages I and II, but not for III and IV. Clément *et al.* (1969) reported the best results following a dose of more than 6 krad. Such a high dose should only be applied to a reduced volume. Urbajtel and Abbatucci (1973) also advocated that at least 6 krad should be administered.

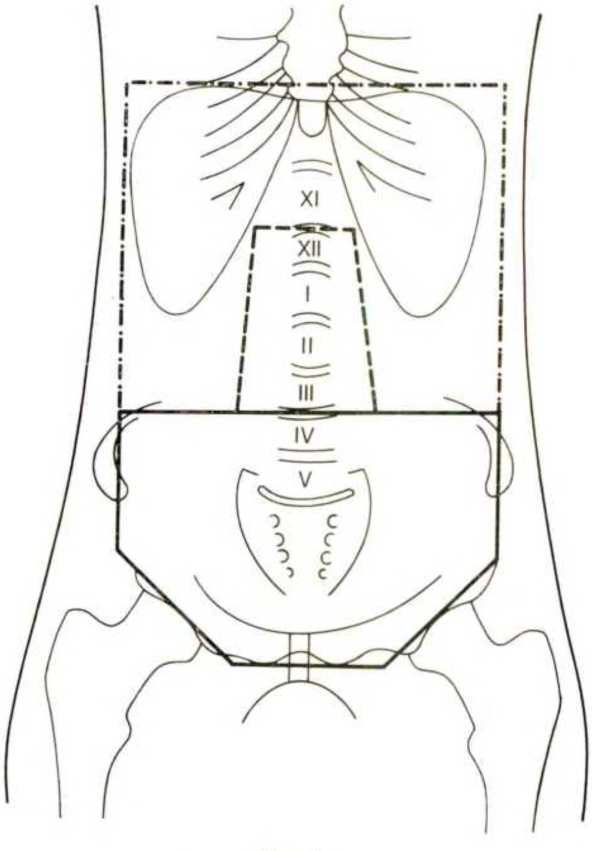

FIG. 1.
Field arrangements: pelvis (—), lumbo-aortic nodes (– –), upper abdomen (–·–·).

The relative number of tumours with a reduction in volume of at least one-third following irradiation increased with the dose received (Fig. 5). The figure shows a clear trend for higher doses to be more effective and suggests that a low dose (2 krad) given to the upper abdomen will be of little benefit. A moving-strip technique was applied in 20 patients but no improvement in results was seen. Radiotherapy applied to the pelvis and the lumbo-aortic nodes resulted in a significantly better three-year survival rate than irradiation restricted to the pelvic area (Fig. 6 left). There was no significant difference between the stage distributions of the two groups and in each of them Stage II patients were the largest category. In mainly Stage III and IV patients treated with combined pelvic and upper abdominal irradiation to a total pelvic dose of 5 krad (33 fractions/45 days) and a total upper abdominal dose of 2·5 or 2 krad (33 fractions/45 days or 27 fractions/37 days), a booster of 2·5 or 3 krad to the lumbo-aortic nodes delivered in the same period and resulting in a total dose of 5 krad (33 fractions/45 days) in this area did not increase the three-year survival rate (Fig. 6 right). The four- and five-year survival rates have been calculated by means of the actuarial method (Berkson and Gage, 1950). The five-year survival rate of Stage I patients appeared to be 68 per cent without significant differences between Ia, Ib and Ic (Fig. 7). No post-operative treatment was given to five Stage Ia patients, in whom the tumour had been totally removed and was not present at the external surface of the capsule: four survived three years or more. Only 26 per cent of Stage II patients lived five years or more and within the first two years 50 per cent were deceased. Very poor results were obtained in Stage III and IV patients as well as in those referred for treatment of a recurrence.

These three groups appeared to have similar survival curves showing a 50 per cent decrease within

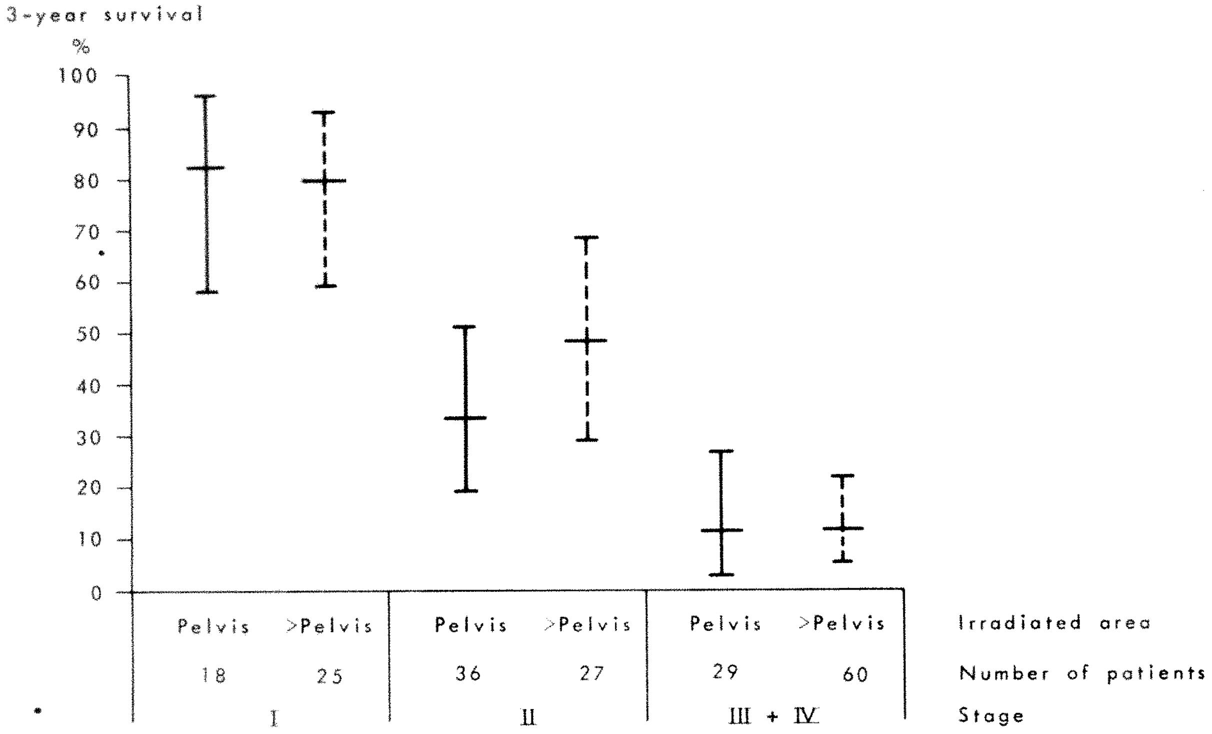

Fig. 2.

Three-year survival rate in relation to the irradiated area: pelvis alone or more than the pelvis (>). The latter category concerns patients irradiated over the pelvis and the lumbo-aortic nodes or over the pelvis and the upper abdomen (with or without lumbo-aortic booster). Error bars indicate 95 per cent confidence limits.

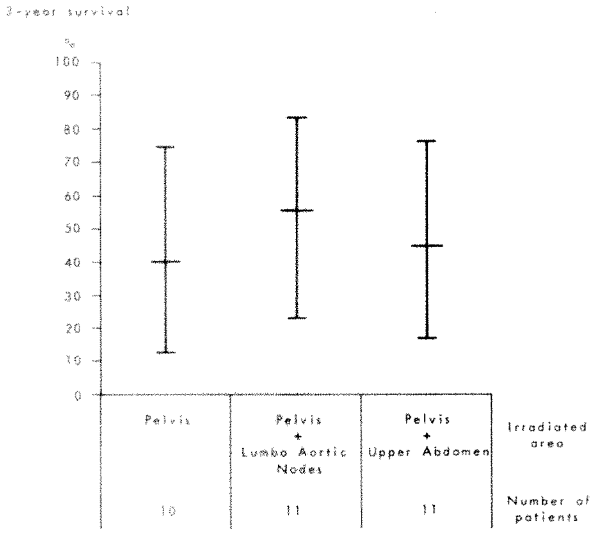

Fig. 3.

Three-year survival rate in relation to the irradiated area in Stage II patients treated with a dose to the pelvis of at least 5 krad. Error bars indicate 95 per cent confidence limits.

eight months and almost no five-year survivals. It is doubtful whether radiation therapy which lasts for about two months can be considered an acceptable palliative approach for these groups.

Concerning the randomized start of chemotherapy following radiotherapy, no significant difference in survival rate could be demonstrated between the two groups (Fig. 8). In the treatment of residual or recurrent disease with chemotherapy, the best results were seen with alkylating agents, Thiotepa and Cyclophosphamide. Data on less frequently occurring ovarian tumours are presented in Tables III and IV; the small numbers precluded statistical analysis. The figures concerning serous carcinoma in Table III are added for comparison.

Discussion

Late diagnosis is the main problem in ovarian cancer. Evaluation of results is difficult because numerous variable factors concerning pathology and mode of treatment produce groups which are too small for statistically reliable conclusions. The following points still need to be investigated in detail.

TABLE III

THREE-YEAR SURVIVAL OF PATIENTS REFERRED TO THE R.R.T.I. BECAUSE OF A MALIGNANT OVARIAN TUMOUR FROM JANUARY 1966 TO JUNE 1972

	Ia	Ib	Ic	I	II	III	IV	R	Total
Serous carcinoma	80%	90%	70%	80%	35%	5%	18%	12%	30%
Mucinous carcinoma	3/8	—	0/1	3/9	0/3	1/6	—	0/4	4/22
Endometrioid carcinoma	3/3	—	1/1	4/4	3/9	1/2	—	0/1	8/16
Mesonephric carcinoma	4/9	—	1/1	5/10	5/8	0/2	—	0/1	10/21
Undifferentiated carcinoma	—	2/2	—	2/2	1/1	1/6	0/1	0/3	4/13
Malignant granulosa cell tumour	3/4	1/1	1/1	5/6	0/6	2/6	—	3/4	10/22
Dysgerminoma	3/3	1/1	—	4/4	—	2/2	1/2	2/2	9/10

TABLE IV

INFREQUENTLY OCCURRING MALIGNANT OVARIAN TUMOURS DIAGNOSED FROM JANUARY 1966 TO JUNE 1972

Histological diagnosis	Stage	Survival in years (L=living †=dead)					
		<1	1	2	3	4	≥5
Malignant teratoma, metastasis neural pattern	III						L
Malignant teratoma, solid pattern	R*	†					
Dermoid cyst with squamous cell carcinoma	II						L
Dermoid cyst with squamous cell carcinoma	II	†					
Dermoid cyst with squamous cell carcinoma	III					L	
Dermoid cyst with squamous cell carcinoma	IV	†					
Dermoid cyst with adenocarcinoma	IV	†					
Dermoid cyst with adeno-squamous cell carcinoma	II	†					
Dermoid cyst with thyroid carcinoma	III				L		
Leiomyosarcoma	R*	†					
Sarcoma (leiomyo or fibro)	II		†				
Mixed mesodermal tumour	R*	†					
Mixed mesodermal tumour	IV	†					
Malignant thecacell tumour	III			†			
Malignant sertolicell tumour	Ib				†		

R* = Referred for treatment of a recurrence.

Pathology

The prognostic significance of:

(1) the capsule being perforated by the surgeon;
(2) the capsule already perforated by tumour growth;
(3) the histological type of the tumour;
(4) the degree of differentiation.

Surgery

The indications for:

(1) unilateral oophorectomy;
(2) omentectomy additional to TAH+BSO;*
(3) Removal of maximum quantity of tumour tissue.

Radiotherapy

The indications for:

(1) irradiation;
(2) the area to be irradiated;
(3) the total dose;
(4) the fractionation.

Chemotherapy

The indications for:

(1) Chemotherapy being used;
(2) Starting immediately after surgery/radiation or being delayed;
(3) A single agent or combined agents;
(4) Continuous or interrupted treatment.

Immunology

(1) The possibilities of earlier detection of the disease and restoration of immunological competence after surgery;
(2) The possible evaluation of changed immunological competence during follow-up leading to the instigation of further treatment measures;
(3) the role of immunotherapy.

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*Total abdominal hysterectomy and bilateral salpingo-oophorectomy.

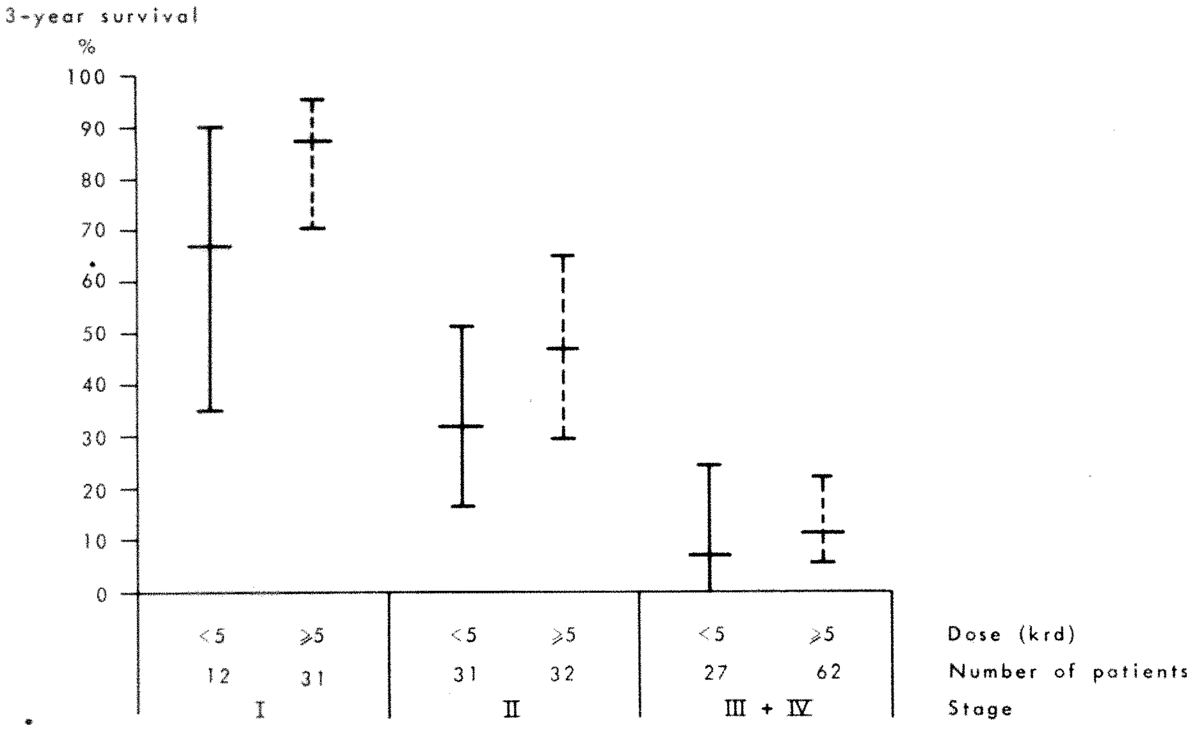

FIG. 4.

Three-year survival rate in relation to the dose applied to the pelvis. Grouping: less than 5 krad (<5) and 5 krad or more (≥5). Error bars indicate 95 per cent confidence limits.

Our knowledge of the epidemiology of these tumours is very poor. Multicentre co-operation is necessary for study of all these problems. The strategy proposed by Young and DeVita (1974) is to establish randomized trials in the search for optimal results. Groups of hospitals should start with the study of only one variable treatment factor. Finally, optimal methods of surgery, radiotherapy, chemotherapy, and immunology can be studied in different combinations according to stage and other characteristics of pathology. Fulfilment of this task will take many years but the high mortality of patients suffering from a malignant ovarian tumour requires a systematic approach to the different problems at regional, national and international levels.

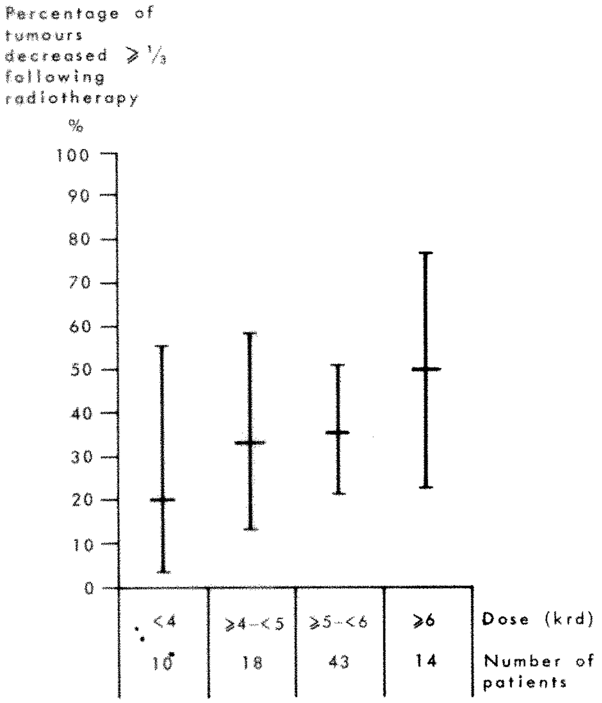

FIG. 5.

Relative number of tumours with a volume reduction of at least 33 per cent following radiotherapy in relation to the dose in krad. Error bars indicate 95 per cent confidence limits.

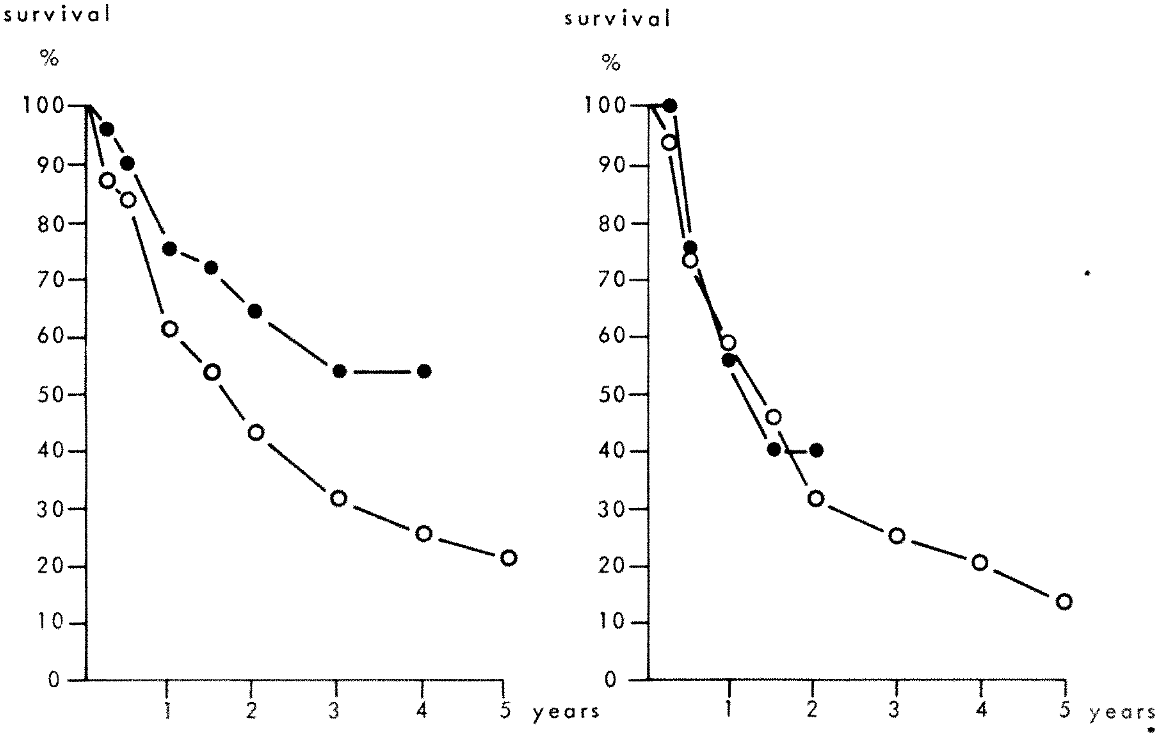

FIG. 6.

Survival curves of patients referred because of a serous ovarian carcinoma from January 1966 to June 1972.
Left: Mainly Stage I and II patients.
Grouping according to the irradiated area: O–O pelvis (100 patients), ●–● pelvis and lumbo-aortic nodes (32 patients).
Right: Mainly Stage III and IV patients.
Grouping according to the applied radiotherapy: ●–● irradiation of the pelvis and the upper abdomen with a booster to the lumbo-aortic nodes (20 patients), O–O irradiation of the pelvis and the upper abdomen without booster to the lumbo-aortic nodes (71 patients).

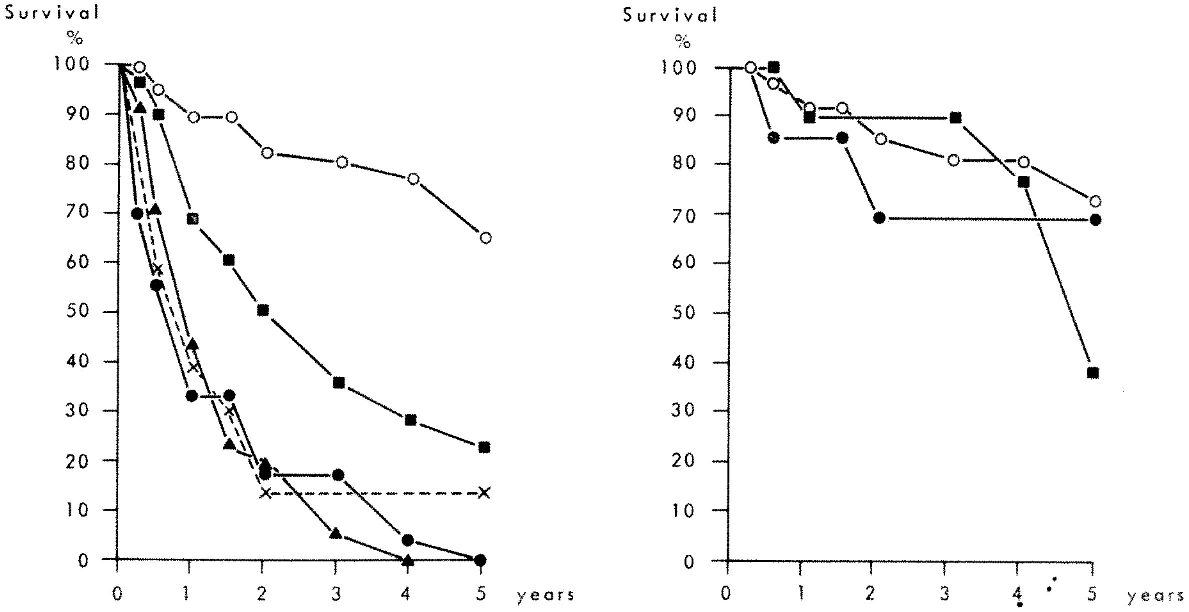

FIG. 7.

Survival curves of patients referred because of a serous ovarian carcinoma.
Left: Subdivision into Stage I (O–O), II (■–■), III (▲–▲), IV (●–●) and patients referred for treatment of a recurrence R (×–×).
Right: Subdivision of Stage I into Stage Ia (O–O), Ib (■–■) and Ic (●–●).

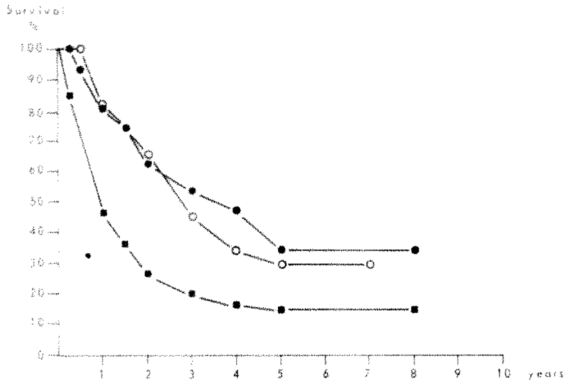

FIG. 8.

Survival curves of patients referred because of a serous ovarian carcinoma from January 1966 to June 1972. *Subdivision:* ○–○ In trial, chemotherapy without delay, 39 patients; ●–● In trial, chemotherapy with delay, 46 patients; ■–■ Not in trial, 169 patients.

REFERENCES

BERKSON, J., and GAGE, R. P., 1950. Calculations of survival rates for cancer. *Proceedings of the Mayo Clinic*, *25*, 270–286.

CLEMENT, R., ALMARIC, R., SPITALIER, J. M., AYMÉ, Y., and ROBERT, F., 1969. Considération sur le traitement des tumeurs malignes de l'ovaire. *Journal de Radiologie et d'Electrologie*, *50*, 235–239.

F.I.G.O. NEWS, 1965. *Journal of the International Federation of Gynaecology and Obstetrics*, *3*, 208–209.

URBAJTEL, M., and ABBATUCCI, J. S., 1973. Problèmes posés par la radiothérapie des épithéliomas germinatifs de l'ovaire. *Journal de Radiologie et d'Electrologie*, *54*, 19–26.

YOUNG, R. C., and DEVITA, V. T., 1974. The design of clinical trials in the therapy of ovarian carcinoma. E.O.R.T.C. Symposium on Clinical Pharmacology with a special reference to cancer at the Institut Jules Bordet, May 13–18, 1974.

Book reviews

Chemotherapy of urogenital tumours. By G. P. Murphy and A. Mittelman, pp. 268, 1975 (Illinois, U.S.A., Charles C. Thomas), $24.50.

This volume is a collection of ten chapters by four authors. It contains 189 pages of text and 27 of references. One-fifth of it is devoted to a chapter on "Animal Models for Experimental Chemotherapy", by M. S. Soloway, much of which is in fact devoted to carcinogenesis. This is a good review paper of the current state of that field of study.

Another fifth is devoted to an excellent review of the oncology of prostatic carcinoma by G. P. Murphy. His detailed presentation of the mechanism of one clinical trial demonstrates the complexity of records required and convinces the reader that a new and more flexible approach will be needed before such a trial could be established in multiple centres.

Murphy is also the author of a good but short chapter on the rare urogenital sarcomas and an excellent account of the use of oncolytics in neuroblastoma. He adds original thought and creative suggestion to a good review.

A. Mittelman gives a good account of the recent status of oncolytic therapy for nephroblastoma and a valuable account of progress in the therapy of adrenal tumours.

His major contribution, however, is a review of the oncology of cancer of the kidney which is stimulating and makes us aware of how far the cult of combination therapy with untried oncolytic drugs has become entrenched whilst other, perhaps more effective, modalities have been evaluated hardly at all. The use of combination hormone therapy in renal cancer is a good example.

A useful review of testicular tumours by S. K. Carter is well presented, but there is little new to say on this subject. The short chapters on carcinomas of the bladder and penis have a heavy and obsolete surgical bias and cannot be taken seriously as modern oncology.

With the last two exceptions, this is a useful collection of papers which should be read by any student of modern oncology and which will probably remain relevant for at least the next two years. If ever there was an argument in favour of the cheap paperback, this is it. Unfortunately it is in fact a bound volume and rather expensive at about £12.

M. L. FENNER.

Cerebral Angiomas. Advances in Diagnosis and Therapy. Edited by H. W. Pia, J. R. W. Gleave, E. Grote, and J. Zierski, pp. x+285, illus., 1975 (West Germany, Springer-Verlag), $23.80.

This book is a report of a symposium held in Giessen in January, 1974. It deals mainly with practical problems of the management of inoperable intracerebral angiomas, but there are interesting chapters on modern radiological techniques used in the diagnosis of cerebral angiomas, including cine, magnification and intra-operative angiography. The contributions of greatest interest to radiologists are probably those on super-selective angiography of the external carotid branches and of embolization of the circulation of lesions supplied by the external carotid branches mainly contributed by Professor Djindjian.

The radiological methods, have, however, all been discussed elsewhere in the radiological literature and the book will be mainly of interest to clinicians, especially surgeons, concerned with the present uses of the modern techniques, some of which are still evolving. Any radiologist doing research on angiomatous malformations will find an extensive and up-to-date bibliography. B. KENDALL.

1976, *British Journal of Radiology*, 49, 533–539

Calculation by computer of dose distributions for superficial gold-198 implants and the derivation of optimized distribution rules

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(*Submitted July, 1975 and in revised form November, 1975*)

ABSTRACT

A computer program has been written which provides two-dimensional visualization of the radiation dose distributions in the treatment surfaces around single-plane gold seed implants. The program was modified in order to investigate the uniformity of dose resulting from various patterns of seed arrangements, and, for a number of sizes of circular implants, practical loading schemes to produce minimum dose variations have been tabulated. Comparisons are made between dose distributions obtained from application of the derived data and those arising from application of the Paterson-Parker rules.

Implantation of ^{198}Au seeds has been carried out at Charing Cross Hospital for many years using a gun of the type developed at the Royal Marsden Hospital. In order to calculate the doses delivered in such techniques it has been customary to obtain tube-shift radiographs of the implants, and hence to construct three-dimensional models showing the relative positions of the grains. The majority of implants are to superficial sites and are of the single-plane type, and where possible have been carried out using the Paterson-Parker principles set out by Meredith (1947). The milligram-hour tables developed for radium by these authors have been used to calculate the effective minimum dose in the treatment plane 0·5 cm distant from the plane containing the grains, the necessary corrections being made to take account of the half-life and specific γ-ray constant of ^{198}Au. For those cases in which the grains lie in an almost perfect plane, this figure alone has been used to specify the dose to the lesion; in instances where the anatomical location of the implant causes the grains to define a non-planar surface, specific sites of interest have been located on the reconstructed models, and the doses at these sites calculated from a summation of the individual doses attributable to each gold grain.

In order to obtain more comprehensive information from the three-dimensional grain co-ordinates (*e.g.* immediate localization of high or low dose regions), a computer program was developed to provide a visual representation in two-dimensions of the dose distributions in the surfaces of interest, *i.e.* two surfaces, each of which is 0·5 cm distant from the surface containing the seeds. The program is written in BASIC and operates on the Kronos time-sharing system of Imperial College, London, via an Olivetti Te. 300 teletypewriter (TTY). The outputs, in the form of hard-copy print-outs obtained directly from the TTY, are full-size displays of the regional variations in dose in which typewriter characters are used to indicate the dose at any particular location.

The decision to build into the program the facility for calculating doses in surfaces was made because practically no single-plane implant has all the grains arranged in a perfect plane. If only dose distributions in planes are considered, then false conclusions may be drawn regarding the accuracy of the implant. An illustration of the possible effects arising from viewing distributions in planes is shown in Fig. 1A. The diagram shows a cross-section through a planar implant which has been carried out to a superficial site, but where the surface curvature has caused the plane of the implant to become deformed in the manner indicated. The whole implant (when considering also its other dimension normal to the page), may approximate to part of the surface of a cylinder or part of the surface of a sphere, but in either case examination of dose distributions in selected planes (as indicated in the diagram) could lead the radiotherapist to feel that the implant is considerably worse than in fact it is, since there would appear on the computer output apparent hot and cold spots which could be confused with those which are genuine, resulting from grains being spaced either too closely or too far apart.

By considering the treatment surface as being 0·5 cm distant from the surface into which the grains have been implanted, a truer picture results, as illustrated in Fig. 1B. Here the seeds do not form quite such a regular contour as before, but nevertheless represent part of a reasonable implant. For the particular cross-section considered, the dotted line indicates the surface of maximum dose (*i.e.* the surface containing the grains). The program as written calculates doses in those surfaces represented by lines S_1 and S_2 in the diagram. The computer output is arranged to show the dose distribution which would be seen in each of the two surfaces when viewed in the direction XX', which is a line normal to the plane (denoted by P in the diagram), which best fits all the grains. In fact the print-outs may be considered to be a simple projection of each of the two dose surfaces in turn onto a plane which is parallel to P, this plane being represented in reality by the paper onto which the output is typed.

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*Copies of the program are available on request from the author at the above address.

CONSTRUCTION OF THE PROGRAM

The important parts of the program are those dealing with the identification of the maximum dose surface containing the gold grains and the two surfaces over which dose calculations are required. The three-dimensional co-ordinates of all the seeds in the implant are entered into the computer, and the flat plane (e.g. P in Fig. 1B) which best fits these sources is calculated by the method of least squares. To make subsequent manipulation of the data easier, this plane is translated and rotated such that it becomes the plane given by $Z=0$, and the seed co-ordinates are transformed accordingly. After this transformation, the new grain co-ordinates still bear the same geometrical relationship to each other as they did before.

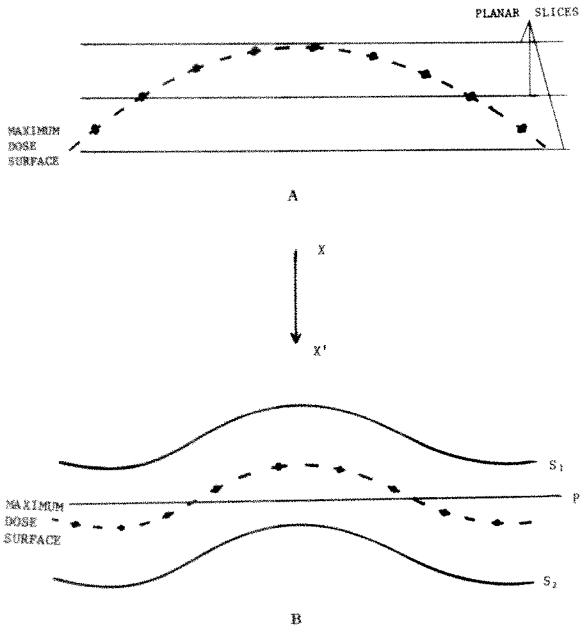


Fig. 1.

Cross-sections through "planar" implants.
(A) Selected planes passing through implant.
(B) Surfaces at fixed distance from maximum dose surface.

The zone of interest in the plane $Z=0$ is taken to be the projected area within the boundary of the implant, together with a peripheral region which extends for at least 2·5 cm outside that boundary. Sites within this region which correspond to TTY character positions (spaced to give ten characters to the inch horizontally on the hard copy and six lines to the inch vertically), are then identified in terms of their (x, y) co-ordinates. Even in the case of a small implant (approximately 2 cm in diameter) this results in the selection of about 330 such sites and, for each of these, the doses at points lying along a line normal to the plane $Z=0$ are calculated at intervals of 1 or 2 mm. With implants containing more than six grains, the doses along each line are determined by summing the contributions only from the six grains closest to the line. The distance interval selected for any one line depends on the magnitude of the value $(Z_{\text{max.}}-Z_{\text{min.}})$, $Z_{\text{max.}}$ being the maximum Z co-ordinate (relative to the plane $Z=0$) of any of the six grains, and $Z_{\text{min.}}$ being the minimum Z co-ordinate. The calculation intervals along each line are normally in 1 mm steps over the range $Z_{\text{min.}}$ to $Z_{\text{max.}}$, except in the rare cases where $(Z_{\text{max.}}-Z_{\text{min.}})>1$ cm, in which case the steps are of 2 mm. This approach is adopted solely to reduce the computation time when running the program; if an implant comprises less than six grains, then all are used at this stage. For the line passing through each site corresponding to a character position, the Z co-ordinate (Z') at which the maximum dose occurs is identified, and thus the maximum dose surface is computed as a series of Cartesian co-ordinates, each of the form (x, y, z'), where (x, y) defines a print position. The two dose surfaces of interest are then described as a series of co-ordinates which take the form $(x, y, z'+0{\cdot}5)$ for one surface, and $(x, y, z'-0{\cdot}5)$ for the other. By writing the program in this way, it is possible to ensure that none of the subsequent dose calculations are made at sites closer than 0·5 cm to the nearest grain.

The calculation of doses in the program are based on a formula due to Meisberger *et al.* (1968). According to these authors, the ratio of the exposure in water to the exposure in air at a point, distance x cm from a point source of ^{198}Au, is given by the polynomial

$$f(x)=A+Bx+Cx^2+Dx^3 \quad . \quad . \quad . \quad (1)$$

where $A=1{\cdot}0306$
$B=-8{\cdot}134\times10^{-3}$
$C=1{\cdot}111\times10^{-3}$
$D=-1{\cdot}597\times10^{-4}$

Equation (1) takes account of the attenuation and build-up effects of radiation from ^{198}Au in water. Using this formula with the value of x set at 0·5 cm yields a figure of 1·027 for the exposure ratio, *i.e.* the exposure in water is 2·7 per cent higher than that which would be obtained by straightforward application of the inverse square law. For values of x greater than about 4·5 cm, the function indicates that use of the inverse square law alone would lead to an overestimation of the exposure at such distances.

The dose D_X (in rad) delivered at a site, distance x cm from a grain, is calculated for each grain in turn by the formula

$$D_X = S \cdot f(x) \cdot \frac{1}{x^2} \cdot \Gamma \cdot T_{\text{eff}} \cdot f_{\text{Au}} \quad . \; . \; . \quad (2)$$

where S is the source strength in mCi/grain,
Γ is the specific γ-ray constant for ^{198}Au (2·35 R/hr^{-1}mC^{-1} at 1 cm),
T_{eff} is the effective life of the isotope (93·5 hours),
and f_{Au} is the rad/röntgen conversion factor at 0·41 MeV (0·968).

Having calculated the dose contributions within the zone of interest in each surface from all the implanted grains, the program smooths out the resulting distribution by means of a nine-point block in which each element of the original dose matrix is replaced by a weighted average of itself and neighbouring elements. The nine-point routine uses the following weighting factors:

$$\begin{matrix} 1 & 2 & 1 & \\ 2 & 4 & 2 & \div 16 \\ 1 & 2 & 1 & \end{matrix}$$

Tests carried out using data from previous implants showed that this method of smoothing is not too severe, and has the effect of giving increased prominence to hot and cold spots which arise in non-perfect distributions. After smoothing, each of the elements in each of the new dose matrices is normalized in terms of the maximum dose found within that matrix, and the doses are then coded in terms of TTY characters. The matrices are then printed out together with $x-y$ reference axes and a key to the character meanings. A typical output for a clinical case is shown in Fig. 2.

The degree of similarity between the two print-outs corresponding to each matrix is in itself an indication of the extent to which individual grains in the implant depart from lying in a smooth, symmetrical surface; the print-outs are generally identical only if the implant is truly planar. The decision as to which of the print-outs is most relevant in a particular case depends largely upon where the seeds have been inserted. If all the grains are at a depth of more than 0·5 cm beneath the tissue surface then both are useful; if the grains tend to be more superficial than this then the print-out labelled "0·5 cm below implant" in Fig. 2 is of more value. In this instance the other print-out is somewhat meaningless since it refers to a surface in air rather than tissue. Prior to inclusion in the patient's notes the computer outputs may be coloured or isodose curves may be added by hand.

DERIVATION OF OPTIMIZED DISTRIBUTION RULES

Inspection of the isodose distributions existing around implants carried out by application of the Paterson-Parker rules indicated the extent to which this system leads to relative overdosing in the central region of the treatment surface and relative underdosing in the peripheral regions. Also clearly observable were the less systematic inhomogeneities existing in the dose patterns around small implants consisting of only a few grains, where, of course, strict interpretation of the Manchester Rules specifying a 2/3 – 1/3 distribution of activity is generally impossible. Part of the program already described was therefore rewritten in order to determine to what extent uniformity of dose was obtainable in practical situations, *i.e.* for given implant sizes and grain activities.

As this was to be a feasibility investigation, which could not take into account all the variables met with in practice, the problem was simplified by imposing a number of restrictions, which were as follows:—

(1) only grains of initial activities 3 and 4 mCi were considered, these being the nominal strengths normally used at this Centre;
(2) only perfectly planar implants were considered;
(3) circular implants only were examined, having diameters ranging from 2 to 6 cm in steps of 0·5 cm (very few implants carried out in this Hospital have mean diameters greater than about 4 cm);
(4) grains in the central region of an implant were to be specifically placed at uniform spacings in a ring of half-diameter and, if necessary, at the centre spot.

The modified program, also in BASIC, was designed to generate its own grain co-ordinates in the plane $Z=0$. For a given diameter of implant, the

```
Y - - - - - - - - - - - - - - - -  Y - - - - - - - - - - - - - - - -
X                                  X
I                                  I
I                                  I
I                                  I
I            00000000000           I             0000000000
I          00000+++++++00          I          000000+++++000
I        0000++-------++00         I        0000++++++++++000
I    .  0000+-HHHH----++000        I       0000++-----++++000
I      0000+-HHHHH----++000        I      000+++-HHHH----++000
I     000+++--HHHH-----+000        I     000+++--HHXHH----+000
I    000+-----HHHHHH--++000        I    000++---HHHHHHH--++000
I    000+--HHHHHHHHH-++000         I    000++--HHHHHHHH-++000
I    000++-HHXHH--HH-+0000         I    000++---HHH----++000
I    000++--HH------+0000          I     000++--H---++++0000
I     00++--+--++++0000            I     000+++---+++00000
I     000++++++0000000             I      00000++++00000
I       00000000000                I       00000000000
I                                  I
I                                  I
I                                  I
I                                  I
```

A

0·5 cm above implant
Maximum dose in surface = 8,238 rad.

B

0·5 cm below implant
Maximum dose in surface = 8,583 rad

Fig. 2.

A typical printout for a clinical case.
Site: gland in neck (left side)
Number of grains: 12
Initial activities (millicuries per grain): 4·1
Range of $X = 10{\cdot}3$ to $13{\cdot}7$ cm
Range of $Y = 4{\cdot}4$ to $7{\cdot}5$ cm
Range of $Z = -1{\cdot}0$ to $0{\cdot}47$ cm

Key

Symbol	Range (per cent of maximum)
X	100 per cent (maximum)
H	80–99 per cent
—	60–79 per cent
+	40–59 per cent
0	20–39 per cent

doses in the plane $Z = 0{\cdot}5$ were calculated using formulae (1) and (2) and, as before, doses were computed at sites corresponding to print positions on the TTY. In this case, print positions lying outside the boundary of the implant were not included for calculation. The standard deviation of the doses in the dose matrix, expressed as a percentage of the average dose to all the sites, was taken to be a measure of the uniformity of a given distribution, *i.e.* the "best" seed arrangement for a given diameter of implant would be the one giving the minimum value of this statistic. The number of sites at which doses were calculated ranged from about 34 for the 2 cm circle to approximately 270 for the 6 cm circle. The nine-point smoothing routine was not utilized in this program.

An example of how the program operated in a particular case is as follows. For a circle of 2·5 cm diameter, the amount of radium required for 1,000 R at the 0·5 cm treatment plane is 159 mg-hours, according to the Paterson-Parker tables. Using the appropriate conversion factors, the total activity of ^{198}Au needed for 6,000 rad is thus 35·3 mCi. If 3 mCi seeds are used, then approximately 12 grains would be required to deliver this dose. In the program, this number of seeds were initially assumed to be uniformly spaced in a 2·5 cm diameter circle, and the dose variations over the plane $Z = 0{\cdot}5$ were determined as described. The distribution of the sources was then altered in accordance with the pattern followed in Table I (in the running of the program, more combinations were tested than are

TABLE I

An example of the sequence of loading distributions tested. The implant consists of a 2·5 cm diameter circle loaded with 12 × 3 mCi grains

Outer ring (2·5 cm diameter)	12	11	10	9	8	7	6	11	10	9	8
Inner ring (1·25 cm diameter)	0	1	2	3	4	5	6	0	1	2	3
Centre	0	0	0	0	0	0	0	1	1	1	1
Standard deviation (expressed as a percentage of the mean dose)	11·53	10·81	7·14	6·03	8·11	11·40	14·51	3·58	8·75	9·41	11·45

TABLE II

Loading systems to give minimum dose variations in a plane 0·5 cm from a plane containing gold grains

A. Approximate activity of grains 3 mCi

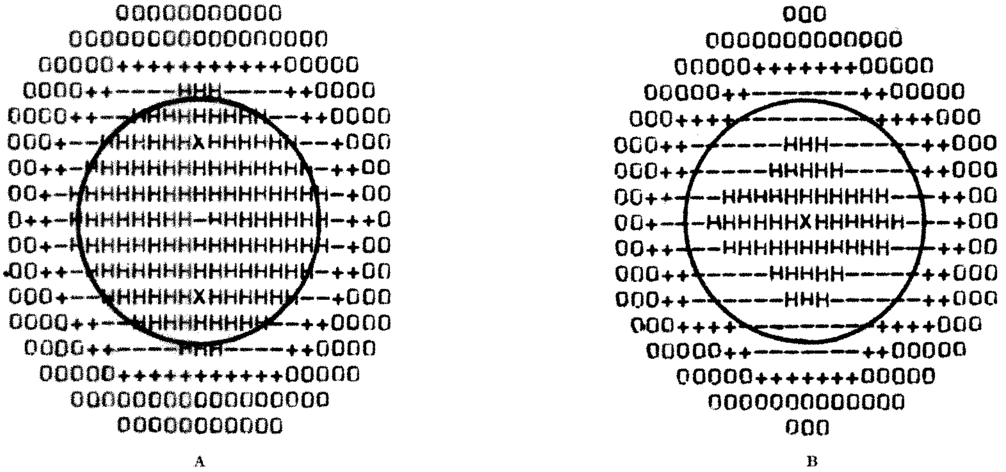
Diameter of circle (cm)	2·0	2·5	3·0	3·5	4·0	4·5	5·0	5·5	6·0
Outer ring	8	11	11	13	15	18	20	22	26
Inner ring of half-diameter	0	0	4	5	6	5	7	8	10
Centre	1	1	0	0	0	1	1	1	1
Total	9	12	15	18	21	24	28	31	37
mCi/grain/6,000 rad	3·02	3·03	2·79	2·83	2·90	3·04	2·96	3·07	2·90
Percentage standard deviation	3·12	3·58	5·01	4·67	4·89	5·27	5·26	6·18	7·13

B. Approximate activity of grains 4 mCi

Diameter of circle (cm)	2·0	2·5	3·0	3·5	4·0	4·5	5·0	5·5	6·0
Outer ring	7	8	10	10	12	13	15	17	20
Inner ring of half-diameter	0	0	0	4	4	5	6	6	7
Centre	0	1	1	0	0	0	0	1	1
Total	7	9	11	13	16	18	21	24	28
mCi/grain/6,000 rad	4·19	3·96	4·16	3·64	3·88	3·99	3·97	3·96	3·86
Percentage standard deviation	6·60	4·50	7·13	7·13	7·50	7·31	7·77	7·77	8·27

shown here). For the circle size considered, the best loading pattern appears to be one in which 11 grains are spaced uniformly in the outer ring and one grain is placed at the centre. Using a total of 12 grains, the Manchester Rules would suggest the use of eight seeds in the outer ring, together with four evenly distributed in the central region. For every loading scheme examined, the dose variations in the treatment plane were noted, and the grain arrangements giving the minimum standard deviations were tabulated. In each case the average dose to the plane at 0·5 cm was calculated, and the activity per grain to give exactly 6,000 rad subsequently determined. The results of doing this are shown in Table II.

As was to be expected, the variations in dose resulting from using 3 mCi seeds in a given size of implant are lower than if a smaller number 4 mCi seeds are employed. Also, although the grain arrangements are different from those specified by the Manchester Rules, it will be noticed that the required activity



A

```
       00000000000
    00000000000000000
  00000+++++++++++00000
 0000++----HHH----++0000
0000++--HHHHHHHHH--++0000
000+--HHHHHHXHHHHHH--+000
00++-HHHHHHHHHHHHHHH-++00
00+-HHHHHHHHHHHHHHHHH-+00
0++-HHHHHHHH-HHHHHHHH-++0
00+-HHHHHHHHHHHHHHHHH-+00
00++-HHHHHHHHHHHHHHH-++00
000+--HHHHHHXHHHHHH--+000
0000++--HHHHHHHHH--++0000
 0000++----HHH----++0000
  00000+++++++++++00000
    00000000000000000
       00000000000
```

B

```
           000
      0000000000000
    00000+++++++00000
  00000++-------++00000
 000++++---------++++000
000++------HHH------++000
000++-----HHHHH-----++000
00++---HHHHHHHHHHH---++00
00+---HHHHHHXHHHHHH---+00
00++---HHHHHHHHHHH---++00
000++-----HHHHH-----++000
000++------HHH------++000
 000++++---------++++000
  00000++-------++00000
    00000+++++++00000
      0000000000000
           000
```

FIG. 3.

Print-out for 4 cm diameter circles.

(A) Distribution arising from optimized 12/4/0 loading scheme. Grain activities 3·88 mCi maximum surface dose 6,655 rad

(B) Distribution arising from Paterson-Parker 10/4/1 loading scheme. Grain activities 4·23 mCi, maximum surface dose 7,993 rad.

Key Symbol	Range (per cent of maximum)
X	100 per cent (maximum)
H	80–99 per cent
—	60–79 per cent
+	40–59 per cent
0	20–39 per cent

per grain to deliver 6,000 rad is in all cases very close to the nominal figure initially used to derive the approximate number of sources required for each of the circles. The spacings of the seeds in the outer ring are remarkably constant for all implant sizes, being 8±1 mm for the 3 mCi grains, and 10±1 mm for the 4 mCi grains.

An indication of the differences between the dose distributions produced by the two alternative loading schemes is demonstrated in Fig. 3, which shows print-outs, for 4 cm diameter circles, obtained from the first program described in this paper. The distribution resulting from the 12/4/0 loading pattern of Table II, with grain activities of 3·88 mCi to deliver a mean dose of 6,000 rad, is shown in Fig. 3a. The maximum dose in the treatment plane is 6,655 rad and the fall off at the edges is to a minimum of 80 per cent of this figure, *i.e.* 5,324 rad. Using corrected mg-hour charts and loading the same size of implant in the form of a Manchester 2/3 – 1/3 distribution consisting of an outer ring, inner ring of half-diameter and centre spot, results in using 15 grains of activity 4·23 mCi in the form of a 10/4/1 loading (Fig. 3b). This leads to a maximum dose of 7,993 rad and a fall off to approximately 60 per cent of this figure, *i.e.* 4,796 rad. If radium were being used, then according to Paterson-Parker application of the Manchester Rules should give an effective minimum dose of 6,000 rad, with an absolute minimum which is 10 per cent less. In the case of the gold seed implant in Fig. 3B, the absolute minimum is 20 per cent less than 6,000 rad, while the central region dose is 33 per cent higher than the average.

DISCUSSION

In recent years, a number of papers have been published on the application of computer techniques to interstitial dosimetry, *e.g.* Jameson *et al.* (1968), Laughlin *et al.* (1963), and Shalek and Stovall (1961). The usual aim is to present the dose distribution as it would appear in a number of representative planar "slices" which may be made through the treated volume. Detailed information may be gained in this manner, and if the implants themselves are designed to be of the "volume" type, then this is probably the best way of extracting information from which the magnitude of the dose variations throughout the treated tissue may be assessed. For single-plane implants, however, more care may be required in the interpretation of such forms of visualization, as is discussed in the Introduction and illustrated in Fig. 1A.

Using the first program described in this paper, such difficulties are largely overcome because the dose distributions examined are not necessarily in a plane, but are in surfaces which are at a fixed distance either side of the surface containing the gold grains. In the planning of a planar implant, the main aim is to deliver a specified dose in a region which is at a given distance (usually 0·5 cm) from the implanted surface. By more precisely identifying the treatment surface, the computer output gives an immediate indication to the radiotherapist of how successful the treatment is in fulfilling this objective.

In the past two years, the program has provided useful visualization of dose distributions around single-plane implants for almost every patient so treated. The only limitation met with in practice is in cases where the site treated exhibits severe surface curvature (*e.g.* in the lateral borders of the tongue or the floor of the mouth), where particular care is required in the interpretation of a two-dimensional projection of such a surface. The same consideration applies in some implants to deep sites (*e.g.* the bladder) where planar implants performed at the time of operation tend to form into volume-type implants when the tissues are stitched. In such cases, an inspection of the grain co-ordinates obtained from the tube-shift radiographs will indicate whether or not the dose calculation would be better carried out using a reconstructed model.

The second program sets out to devise loading schemes for circular implants which, if correctly followed in practice, will deliver as uniform a dose as possible in the treatment surface for a given number of gold grains. Meredith *et al.* (1966) have investigated the applicability of the Paterson-Parker rules to a number of other clinically useful isotopes (^{137}Cs, ^{192}Ir and ^{198}Au), and have concluded that each could be used as a satisfactory alternative to radium. However, the distribution rules derived here do not depend in any way on the inherent assumptions initially made regarding radium dosimetry in the compilation of the Manchester Rules. The use of a computer has enabled a large number of discrete loading arrangements to be examined in a "trial and error" approach, from which selection of an optimal distribution of sources for a given size of implant is based solely on the uniformity of the associated dose pattern. Also, by defining fairly precisely where the central grains should be located (*e.g.* how many should be evenly spaced in the circle of half-diameter, and whether or not a central source is required), the problem of randomly allocating grains in the central region is largely overcome and the chance of inadvertently obtaining extreme local dose variations is reduced.

It may be argued that some small tumours have a cross-sectional form which is lens-shaped rather than rectangular and that the isodose contours around an implant should take this shape also. In order to achieve such distributions, alternative proposals for the arrangement of *radium needles* have been made by Howells and Oliver (1964), but for small implants, even the unmodified Paterson-Parker rules, when applied to gold seeds, lead to distributions giving a higher than average dose in the central region of the treatment plane, with a corresponding lower dose towards the perimeter. However, it is particularly the case for these small implants, where only a few grains are employed, that the true shape of the isodose curves is strongly dependent on the relative positioning of the grains in the central region.

The results here describe loading schemes which reduce the likelihood of obtaining large local dose variations in the treatment plane, but in some cases this may be at the expense of losing what may have been a more or less ideal lens-shaped isodose structure. The decision as to whether an optimized rectangular distribution is preferable or not to one which is lens-shaped with larger local inhomogeneities is a clinical one which can only be made for individual lesions, taking account of their shape and anatomical location.

ACKNOWLEDGMENTS

I wish to express my thanks to Dr. W. E. Liversage of the Radiation Physics Department, St. Bartholomew's Hospital, for helpful criticisms and suggestions made during the development of the programs. Also, I am indebted to Dr. N. Howard, Consultant Radiotherapist, Charing Cross Hospital, for the interest he has shown in this work.

REFERENCES

HOWELLS, R. and OLIVER, R., 1964. Single-plane implants using needles of the same uniform linear activity. *British Journal of Radiology*, *37*, 844–846.

JAMESON, D. G., CAMPION, J. M., and TREVELYAN, A. 1968. A computer system for interstitial and intracavitary dose calculations. *British Journal of Radiology*, *41*, 696–700.

LAUGHLIN, J. S., SILER, M. S., HOLODNY, S. C., and RITTER, F. W., 1963. A dose description system for interstitial radiation therapy. *American Journal of Roentgenology*, *89*, 470–490.

MEISBERGER, L. L., KELLER, R. J., and SHALEK, R. J., 1968. The effective attenuation in water of the gamma rays of Gold-198, Iridium-192, Caesium-137, Radium-226 and Cobalt-60. *Radiology*, *90*, 953–957.

MEREDITH, W. J. (ed.), 1947. *Radium Dosage* (E. and S. Livingstone, Edinburgh).

MEREDITH, W. J., GREEN, D., and KAWASHIMA, K., 1966. The attenuation and scattering in a phantom of gamma rays from some radionuclides used in mould and interstitial gamma-ray therapy. *British Journal of Radiology*, *39*, 280–286.

SHALEK, R. J., and STOVALL, M. A., 1961. A calculation of isodose distributions in interstitial implantants by computer. *Radiology*, *76*, 119–120.

1976, *British Journal of Radiology*, *49*, 540–546

A quantitative assessment of femoral head activity using ^{99}Tc^{m}-polyphosphate and a computer data collection system

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(Received April, 1975 and in revised form October, 1975)

Abstract

Abnormal femoral head activity in Legg-Calve-Perthes' disease has been measured using ^{99}Tc^{m}-polyphosphate and a gamma camera/computer data collection system. A reference point on the data matrix, which is unaffected by the disease, is used for deriving comparative uptake ratios in each femoral head. The reference point remains unaltered after surgical procedures or short intervals between follow-up studies. Early abnormality can be measured in both unilateral and bilateral femoral head pathology.

The importance of assessing femoral head vascularity and osteogenic activity in children and adults has been stressed by a number of workers (Tucker, 1949; Trueta, 1957; Ponseti and Cotton, 1961; Richards and Brookes, 1969; Kemp, 1973). The introduction of bone sampling techniques by Tucker (1950), using ^{32}P, significantly improved the early diagnosis of femoral head disease and provided a more sensitive method for detection. More recent advances in this field have allowed external detection and imaging using gamma-emitting radioisotopes (Riggins *et al.*, 1974; Bohr, 1973). Further improvements in gamma-camera image quality have become possible with the introduction of ^{99}Tc^{m}-phosphate complexes (Subramanian *et al.*, 1971; Subramanian and McAfee, 1971). These have important advantages over other bone seeking radionuclides (Rayudu *et al.*, 1972; Krishnamurphy *et al.*, 1973; Barrett and Smith, 1974; Hardy and Newble, 1974) and consequently have become popular agents for femoral head imaging in adults (Desaulniers *et al.*, 1974; Webber *et al.*, 1974) and children (Bell *et al.*, 1972; Danigelis *et al.*, 1974; Blair *et al.*, 1972; Schuler *et al.*, 1972).

Much of the diagnostic information obtained from femoral head scanning has been derived from qualitative displays. It is the purpose of this paper to describe a sensitive quantitative technique which has been used successfully in the diagnosis of Legg-Calve-Perthes' disease.

Polyphosphate localization

Initial uptake of polyphosphate in the skeleton is dependent on regional vascular supply (Desaulniers *et al.*, 1974; Webber *et al.*, 1974; Thrall and Geslien, 1974); indeed, polyphosphate levels in superficial hyperaemic tissue can obscure bone activity (Thrall and Geslien, 1974). However, the later stages of polyphosphate uptake involve a trapping mechanism by the bone hydroxyapatite, since sodium pertechnetate *per se* shows very little affinity for the bone mineral (Desaulniers *et al.*, 1974). At this stage the chain length of the polyphosphate molecule is critical if optimum mineral trapping is to be achieved, and recent assessment of *in-vivo* trapping efficiency has shown that the optimum chain lengths are 30–60 phosphate units long (King *et al.*, 1973). Experiments have been performed to demonstrate the relationship between exchangeable and incorporated isotope, using a commercially available polyphosphate (Duphar). Studies so far, using a technique described by Elves (1974), have suggested that at four hours 30 per cent of the activity is due to loose binding rather than accretion.

Autoradiographic techniques (Tilden *et al.*, 1973) have shown that the ^{99}Tc^{m}-polyphosphate complex is localized in precise patterns, indicating both an affinity for mature bone mineral structures and areas of osteocyte concentration where active mineral turnover would be expected. Enzyme activity, associated with mineral metabolic pathways, should be another trapping mechanism for polyphosphate complexes. Supporting this hypothesis, concentrations have been seen in non-bony regions of mammary tissue rich in phosphatase (Zimmer *et al.*, 1974) and in lung tumours containing calcitonin (Merrick, 1974).

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From these observations it would seem that the factors leading to polyphosphate localization in bone are:

(1) vascularity;
(2) loose binding;
(3) enzyme activity;
(4) mineral trapping by the bone hydroxyapatite.

Application to femoral head studies

The localization of ${}^{99}Tc^{m}$-polyphosphate in the femoral head is sensitive to pathological variations (Webber *et al.*, 1974; Bell *et al.*, 1972; Danigelis *et al.*, 1974). A quantitative assessment of femoral head activity in children with Perthes' disease should provide an accurate comparative measure aiding both diagnosis and follow-up.

Quantitative assessments of bone activity at other sites using data collected by computer (Stevenson *et al.*, 1973; Genant *et al.*, 1974) and multichannel analyser (Citrin *et al.*, 1974) have been reported. Bohr (1973) has studied the revascularization of the femoral head in Perthes' disease using densitometry and ${}^{18}F$ scintigraphy. Our quantitative computer method, using ${}^{99}Tc^{m}$-polyphosphate, measures the change in vascularity and reactive new bone formation.

Tucker (1950) noted that dead bone in the femoral head may attract calcium salts from surrounding fluids. This ionic concentration may also contribute to the increased polyphosphate uptake in this region that we and other workers have observed (Webber *et al.*, 1974).

METHODS AND MATERIALS

A sample group of 18 children of both sexes, aged between four and ten years, who were either suspected or confirmed to have Perthes' disease, was investigated. Polyphosphate bone scans were performed:

(1) as a diagnostic procedure;
(2) prior to corrective surgery;
(3) three months after surgery;
(4) in some cases, six months after surgery.

A number of normal hips formed a control group. These were taken from children having polyphosphate bone scans for other pathology. Both postero-anterior (PA) and antero-posterior (AP) radiographs were taken on the same day as the radioisotope study.

The weights of the children were known and an intravenous dose of 140 μCi/kg was administered. Three hours after the injection the patient, having emptied his bladder, was placed supine under a five-inch double-headed scanner (Ohio Nuclear 84) and photoscans from the pelvic area obtained. Standard low energy collimators were used, each scan taking 35–40 minutes for completion. The same patient position was maintained for a gamma-camera quantitative study so that the femoral head region was in the upper half of the camera field of view and the bladder activity adequately shielded with a small circle of lead sheet. A total of 500,000 counts was collected by the computer in about three minutes, using a high sensitivity, low energy, parallel hole collimator.

The gamma camera used in these studies (Nuclear Enterprises Mk. III) was interfaced to a PDP 11/45 computer (Dowsett and Roberts, 1974) and the data collection carried out in frame mode using a 64×64 matrix. The reliable quantitation of this data depended on the choice of a suitable reference site in order that comparisons between normal and abnormal femoral heads could be made. Our choice of this reference site was difficult due to the heterogeneous uptake in the complex structure of the pelvic girdle and lower spine. A multiple contour plot of this area, shown in Fig. 1, illustrates this point. The femoral head itself was rejected as a possible reference source, as bilateral involvement is possible. After careful study the most reliable

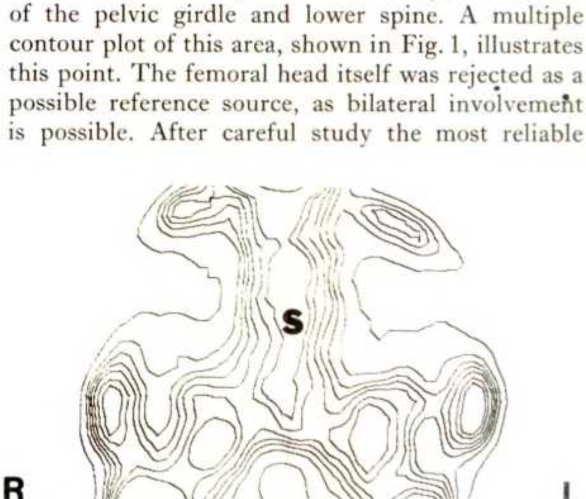

FIG. 1.

Contour plot of the antero-posterior pelvic area from data collected by the computer. The contours range from 100 to 500 counts per matrix area illustrating the complex uptake pattern in a child's pelvic region. The shielded bladder region (B), the two femoral heads (F), with the right side abnormal, and the sacral area (S) are shown. Sharp density changes throughout this region make it unsuitable for reference siting.

reference point within the camera field of view was found to be on the femoral shaft.

A Fortran programme was used to select automatically the maximum count area for each femoral head present in the data matrix. A five-point mean value was then calculated from each maximum and its surrounding areas and this centroid value was compared to the reference value taken from the upper femoral shaft region. This gave an uptake ratio for each femoral head. Of the several methods investigated, the most reliable reference point on the femoral shaft was 15 matrix areas* below the femoral head maximum on the normal side; three vertical areas centred about this point gave the reference mean value used throughout the analysis. The approximate anatomical position of this reference site is indicated with an arrow on the right femoral shaft of scintiphoto Fig. 6B. The two ratios, obtained from the reference mean and the two femoral head centroid values, give a comparative measure for the femoral head activities. Femoral head activity contours are also shown on the programme display by noting all matrix areas which have a count greater than the femoral shaft reference value multiplied by an empirical constant of 2·5. These contours indicate the extent of the activity in each femoral head. A flowchart for the entire programme is shown in Fig. 2.

RESULTS

The normal femoral shaft reference mean from a number of patients was tested for reliability over a follow-up period. No significant difference was found between sets of normal shaft references obtained on separate occasions; the t value was 0·705 ($t_{0\cdot05}=2\cdot07$) and the difference between sample variances was small, F value 1·05 ($F_{0\cdot05}=3\cdot24$). Therefore the reproducibility of a normal reference in the same patient during a typical follow-up period was adequate for reliable quantitative comparisons. Maintaining a precise anatomical position for the reference site, in different patient sizes, has not been found necessary.

The mean values of the "normal femoral head: normal shaft" ratio, for each age group seen in this study, are shown plotted in Fig. 3, together with their standard deviations. Clinically abnormal

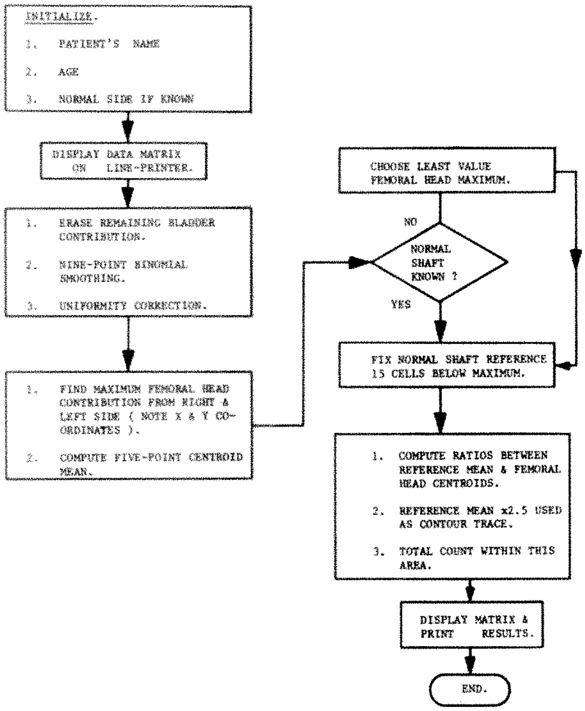
INITIALIZE.
1. PATIENT'S NAME
2. AGE
3. NORMAL SIDE IF KNOWN
DISPLAY DATA MATRIX ON LINE-PRINTER.
1. ERASE REMAINING BLADDER CONTRIBUTION.
2. NINE-POINT BINOMIAL SMOOTHING.
3. UNIFORMITY CORRECTION.
1. FIND MAXIMUM FEMORAL HEAD CONTRIBUTION FROM RIGHT & LEFT SIDE (NOTE X & Y CO-ORDINATES).
2. COMPUTE FIVE-POINT CENTROID MEAN.
CHOOSE LEAST VALUE FEMORAL HEAD MAXIMUM.
NO
NORMAL SHAFT KNOWN ?
YES
FIX NORMAL SHAFT REFERENCE 15 CELLS BELOW MAXIMUM.
1. COMPUTE RATIOS BETWEEN REFERENCE MEAN & FEMORAL HEAD CENTROIDS.
2. REFERENCE MEAN x2.5 USED AS CONTOUR TRACE.
3. TOTAL COUNT WITHIN THIS AREA.
DISPLAY MATRIX & PRINT RESULTS.
END.

FIG. 2.

The flowchart of the computer programme used in the femoral head analysis. The data matrix is printed out twice; first to check coordinates of the bladder remnants for erasing; secondly, at the finish of the analysis, when the activity contours are shown as blank areas.

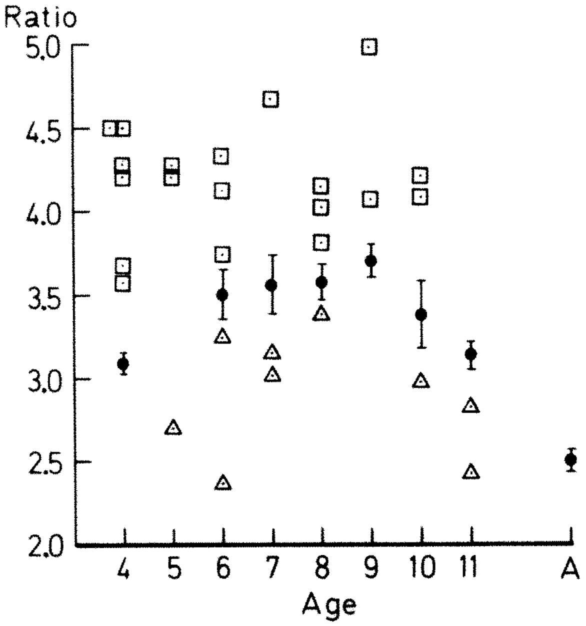

FIG. 3.

A plot of normal femoral head ratios (mean ± one standard deviation) for separate age groups from 4 to 11 years (●). Cases of Perthes' disease (□) show consistently high uptake values. The lower values (△) following surgery have decreased femoral head activity. The adult normal value (A) is shown for comparison.

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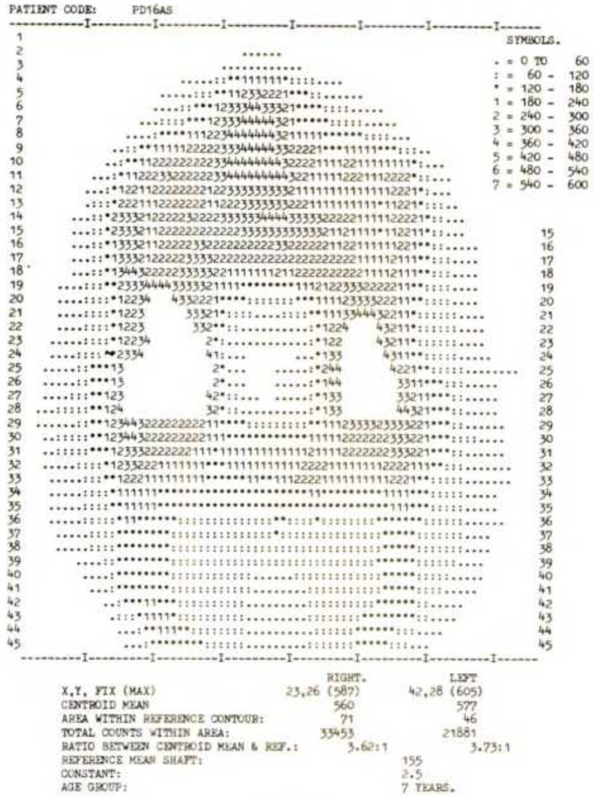
*One matrix area equivalent to 4 mm on the gamma camera face.



```
PATIENT CODE:     PD16AS

SYMBOLS.
. = 0 TO     60
: =   60 -  120
* =  120 -  180
1 =  180 -  240
2 =  240 -  300
3 =  300 -  360
4 =  360 -  420
5 =  420 -  480
6 =  480 -  540
7 =  540 -  600

                                          RIGHT.          LEFT
X,Y, FIX (MAX)                         23,26 (587)     42,28 (605)
CENTROID MEAN                              560              577
AREA WITHIN REFERENCE CONTOUR:              71               46
TOTAL COUNTS WITHIN AREA:                33453            21881
RATIO BETWEEN CENTROID MEAN & REF.:          3.62:1           3.73:1
REFERENCE MEAN SHAFT:                               155
CONSTANT:                                           2.5
AGE GROUP:                                          7 YEARS.
```

FIG. 4.

Quantitative analysis from a normal seven-year-old girl. Both femoral heads are within the normal range for this age group. The data print-out beneath the display consists of:

(1) *X, Y fix(max)*: Giving the X,Y co-ordinates of the right and left maximum in the original data matrix.

(2) *Centroid mean*: Computed from the maximum value and adjacent four cells.

(3) *Area within the reference contour*: Number of matrix cells within the reference contour, computed as (6) multiplied by (7) described below.

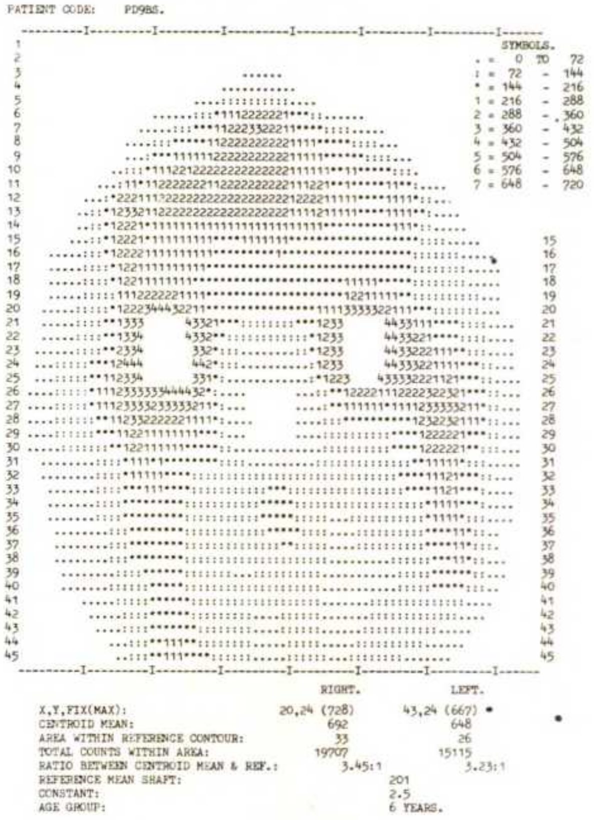
(4) *Total counts within area*: The total count within contour (3) above.

(5) *Ratio between centroid mean and ref.*: Ratio formed between right and left mean values from (2) and (6).

(6) *Reference mean shaft*: Mean value formed from 3-point vertical group fixed 15 cells below (1) on the normal shaft.

(7) *Constant*: Used to compute reference contour in (3).

(8) *Age group*: Age of patient requested at programme initiation.



```
PATIENT CODE:     PD9BS.

SYMBOLS.
. =    0  TO    72
: =   72   -   144
* =  144   -   216
1 =  216   -   288
2 =  288   -   360
3 =  360   -   432
4 =  432   -   504
5 =  504   -   576
6 =  576   -   648
7 =  648   -   720

                                        RIGHT.          LEFT.
X,Y,FIX(MAX):                        20,24 (728)     43,24 (667)
CENTROID MEAN:                           692              648
AREA WITHIN REFERENCE CONTOUR:            33               26
TOTAL COUNTS WITHIN AREA:              19707            15115
RATIO BETWEEN CENTROID MEAN & REF.:        3.45:1           3.23:1
REFERENCE MEAN SHAFT:                             201
CONSTANT:                                         2.5
AGE GROUP:                                        6 YEARS.
```

FIG. 5.

The quantitative analysis showing an abnormally low ratio on the left side due to a previous osteotomy. The right femoral head shows a normal ratio for this age group (six years). The photoscan and gamma-camera picture from this case are shown in Fig. 6.

femoral heads are seen to fall significantly outside the normal range for each age group. The analytical display for a normal seven-year-old child is shown in Fig. 4 where both the femoral head activity ratios are within the normal range for this age group. Figure 5 demonstrates the sensitivity of the computer analysis on a patient following femoral osteotomy. The photoscan and gamma-camera scintiscan are shown in Fig. 6A, B. Here it can be seen that the osteotomy of the left femur has reduced the femoral head activity ratio below the expected normal value for this age.

The ability to detect bilateral femoral head abnormality was tested by fixing a femoral-shaft reference point on both femurs using the normal and early abnormal femoral head maxima from a mixed group of children. Shaft references found from normal femoral head co-ordinates were compared with opposite shaft references fixed from the abnormal head co-ordinates. Comparing these two means gave a t value of 0·654 ($t_{0\cdot05}=2\cdot101$) and an F value of 1·05 ($F_{0\cdot05}=2\cdot22$) suggesting that in the early stages of the disease both abnormal and normal femoral head maxima had similar origins within the resolution of our gamma camera. Therefore in cases presenting possible bilateral Perthes' disease, reference shaft values derived from co-ordinates of either abnormal femoral head maxima produce uptake ratios of diagnostic value. Figure 7 shows the print-out from a case of bilateral Perthes'

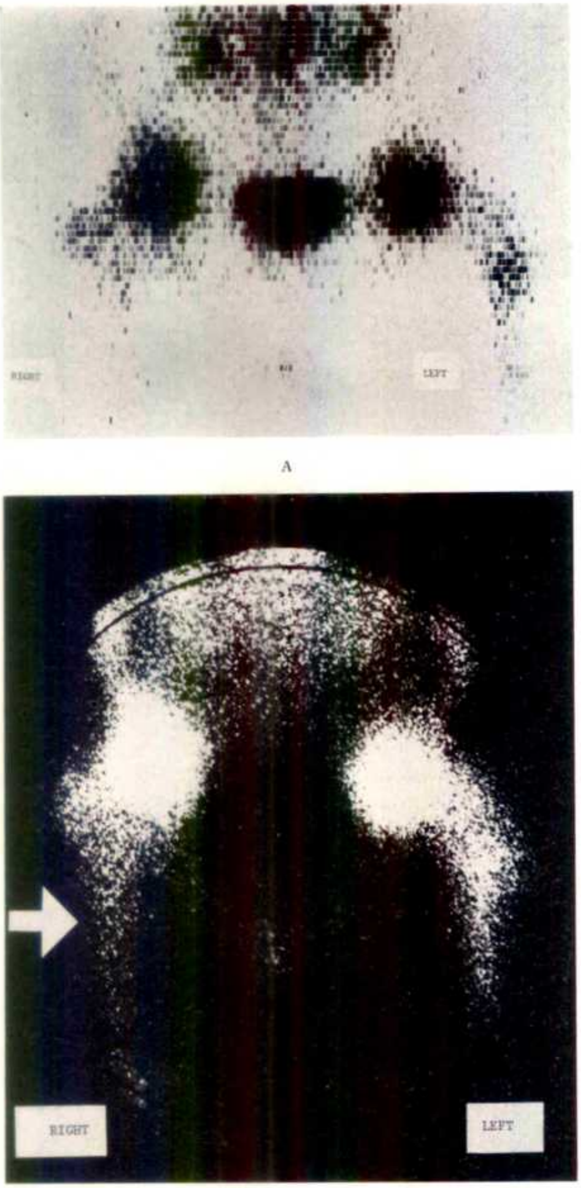
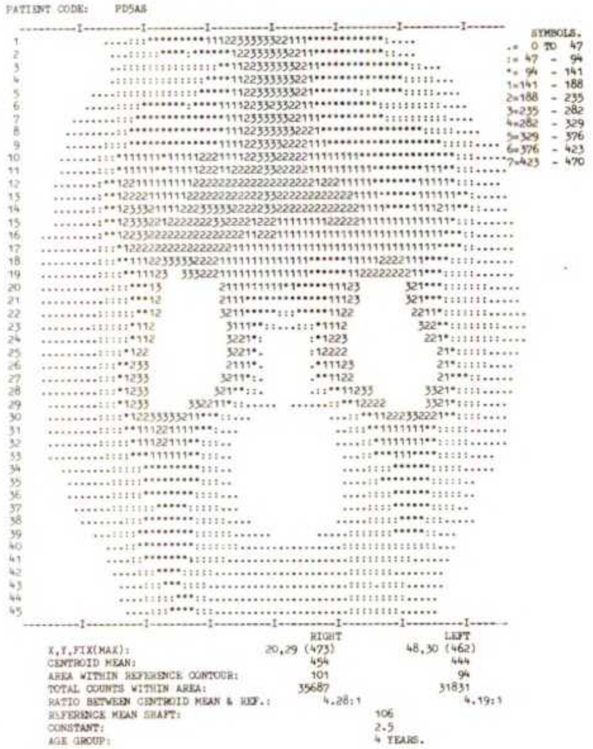


Fig. 6.

(a) Combined antero-posterior and postero-anterior rectilinear scan of a healed osteotomy site. Right femoral head and shaft are normal.

(b) Gamma-camera antero-posterior scintigram of the same patient. Femoral heads of this patient are sited in the top half of the camera field. The normal shaft reference regions are situated away from the crystal edge (arrowed).

where both ratios are significantly high for this age group.



```
PATIENT CODE:    PD5AS

                                                    SYMBOLS.
                                                    .=  0 TO  47
                                                    :=  47 -  94
                                                    *=  94 - 141
                                                    1=141  - 188
                                                    2=188  - 235
                                                    3=235  - 282
                                                    4=282  - 329
                                                    5=329  - 376
                                                    6=376  - 423
                                                    7=423  - 470

                                         RIGHT           LEFT
X,Y,FIX(MAX):                         20,29 (473)     48,30 (462)
CENTROID MEAN:                            454             444
AREA WITHIN REFERENCE CONTOUR:            101              94
TOTAL COUNTS WITHIN AREA:               35687           31831
RATIO BETWEEN CENTROID MEAN & REF.:       4.28:1          4.19:1
REFERENCE MEAN SHAFT:                           106
CONSTANT:                                       2.5
AGE GROUP:                                      4 YEARS.
```

Fig. 7.

Bilateral abnormal uptake in femoral head region where the qualitative information was conflicting due to equally high uptakes on both sides. Both femoral heads, however, gave significantly high ratio values from the computer analysis.

Discussion

The scan data display dimensions have been adjusted during print-out to correct the distortion of the line-printer character/line distances. For this reason X–Y co-ordinates of the two maxima together with the measured area size, calculated from the stored data matrix and then printed beneath the display, do not conform with the display dimensions. Count density symbols, shown in the display, are allocated before areas within the reference contour are identified and erased, so maintaining consistent symbol scale references.

Area of involvement within the calculated activity contour, together with the count total within this area, has been retained on the display in spite of its limited quantitative value, as it does indicate the extent of femoral neck involvement.

Patient siting, with respect to the camera, is important as crystal edge artefacts can cause non-uniformity and spatial distortions in the femoral shaft reference areas. For this reason the femoral heads are ideally situated well into the top half of the camera field, allowing the greater part of the remaining lower field for the shafts themselves. This position is shown in Fig. 6b.

The small hip dimensions of children allow both femoral heads to lie within the camera view using the parallel hole collimator. Data from normal adult femoral heads have been collected on separate computer core matrices for comparisons.

Data from rectilinear scanners could probably be used in this analysis. Scanners, unlike gamma cameras, are not fixed-count dependent or affected by edge-of field artefacts, so bladder shielding and patient positioning would not be important. However, as speed of data collection was important in our study, the patients showing the typically high degree of fidgeting for this age group, gamma-camera imaging was chosen.

Technetium-labelled diphosphonate may give a better performance in this analysis, due to its more selective uptake behaviour and lower blood background (Zimmer *et al.*, 1974). This is being investigated.

With increasing numbers of paediatric femoral head bone scans being analysed, larger sample sizes for each age group should provide better definition of normal ratios, thus further improving diagnostic sensitivity. A full clinical assessment of this analysis is being prepared.

CONCLUSION

Application of quantitative techniques to children's femoral head studies using ^{99}Tc^{m}-Sn: polyphosphate and a gamma camera/computer system, has shown promising diagnostic results. Providing the position of the patient is carefully chosen and bladder shielding maintained, the reliable uptake characteristics of ^{99}Tc^{m}-Sn: polyphosphate allow accurate quantitative measurements.

Improved diagnostic sensitivity has been obtained from the system when compared with purely qualitative radiographs, rectilinear photoscans or gamma-camera scintiscans. Reliable reference points can be selected from the femoral shaft and used to measure abnormal uptakes in the femoral heads themselves. Bilateral abnormalities which may not be evident from qualitative displays alone, can be demonstrated with this technique.

The Fortran computer programme, which has been developed for this analysis, is straightforward and requires only a line-printer or teletype for displaying the results.

ACKNOWLEDGMENTS

The authors wish to thank John S. Clifton for his advice and support throughout the project together with Steven M. Pizer and Andrew Todd-Pokropek for their help with image data statistics. The invaluable patient care given by Diana Spencer, Susan Nevin and Jennifer Bevington was much appreciated as was the efficient preparation of the manuscript by Vivien Wood.

The computer used for this study was provided by the Department of Health and Social Security (Grant A/C334/BG4/3).

REFERENCES

BARRET, J. J., and SMITH, P. H. S., 1974. Bone imaging with ^{99m}Tc-polyphosphate: a comparison with ^{18}F and skeletal radiography. *British Journal of Radiology, 47,* 387–392.

BELL, E. G., BLAIR, R. J., SUBRAMANIAN, G., and MCAFEE, J. G., 1972. Evaluation of ^{99m}Tc-polyphosphate as a pediatric bone scanning agent (abs). *Journal of Nuclear Medicine, 13,* 412.

BLAIR, R. J., BELL, E. G., SUBRAMANIAN, G., and MCAFEE, J. G., 1972. Evaluation of ^{99m}Tc-polyphosphate imaging for non-neoplastic skeletal disease (abs). *Journal of Nuclear Medicine, 13,* 414.

BOHR, H., 1973. Densitometry and ^{18}F scintigraphy in the study of the revascularization of the femoral head in Coxa-Plana (C-T). *Acta Orthopaedica Scandinavica, 44,* 417–425.

CITRIN, D. L., BESSENT, R. G., TUOHY, J. B., GREIG, W. R., and BLUMGART, L. H., 1974. Quantitative bone scanning: a method for assessing response of bone metastases to treatment. *Lancet, 1,* 1132–1133.

DANIGELIS, J. A., FISHER, R. L., and OZONOFF, M. B., 1974. ^{99m}Technetium polyphosphate bone imaging in Legg-Perthes' disease (abs). *Journal of Nuclear Medicine, 15,* 485.

DESAULNIERS, M., FUKS, A., HAWKINS, D., LACOURCIERE, Y., and ROSENTHAL, L., 1974. Radiotechnetium-polyphosphate joint imaging. *Journal of Nuclear Medicine, 15,* 417–423.

DOWSETT, D. J., and ROBERTS, K., 1974. Long distance transmission of analog gamma camera signals. *Journal of Nuclear Medicine, 15,* 896–899.

ELVES, M. W., 1974. An evaluation of the use of strontium-85 for the assessment of experimental bone grafts. *Acta Orthopaedica Scandinavica, 45,* 641–651.

GENANT, H. K., BAUTOVICH, G. J., LATHROP, K. A., and HARPER, P. V., 1974. *In vivo* study of factors influencing skeletal uptake of bone seeking radionuclides (abs). *Journal of Nuclear Medicine, 15,* 493.

HARDY, J. G., and NEWBLE, G. M., 1974. The detection of bone lesions using ^{99}Tc^{m}-labelled polyphosphate. *British Journal of Radiology, 47,* 769–774.

KEMP, H. B. S., 1973. Perthes' disease: an experimental and clinical study. *Annals of the Royal College of Surgeons of England, 52,* 18–35.

KING, A. G., CHRISTY, B., HUPF, H. B., and BLOCK, R. E., 1973. Polyphosphates: a chemical analysis of average chain length and the relationship to bone deposition in rats. *Journal of Nuclear Medicine, 14,* 695–698.

KRISHNAMURPHY, G. T., WALSH, C. F., KINNEY, B. J., STICHLER, S., SHOOP, L. E., BERGER, H. G., and BLAHD, W. H., 1973. Comparison of ^{99m}Tc-polyphosphate bone images obtained with scanner and a scintillation camera equipped with high resolution and high sensitivity collimators (abs). *Journal of Nuclear Medicine, 14,* 419.

MERRICK, M. V., 1974. Bone scanning: a review article. *British Journal of Radiology, 48,* 327–351.

PONSETI, I. V., and COTTON, R. L., 1961. Legge-Calve-Perthes' disease—pathogenesis and evolution. *Journal of Bone and Joint Surgery, 43A,* 261–274.

RAYUDU, G. V. S., TROUTT, E. D., and FORDHAM, E. W., 1972. A comparison of ^{99m}Tc-Sn(II) polyphosphates, 87mSr and 18F in bone imaging. *Journal of Nuclear Medicine, 13,* 462.

RICHARDS, D. J., and BROOKES, M., 1969. Bone vascularity following experimental osteotomy (abs). *Journal of Bone and Joint Surgery 51B,* 568.

RIGGINS, R. S., DENARDO, G. L., D'AMBROSIA, R., and GOLDMAN, M., 1974. Assessment of circulation in the femoral head by fluorine-18 scintigraphy. *Journal of Nuclear Medicine 15*, 183–186.

Schuler, S. E., Weiss, T. E., and Aprill, C. N., 1972. Peripheral joint imaging in pediatrics (abs). *Journal of Nuclear Medicine, 13*, 466.

Stevenson, J. S., Bright, R. W., Dunson, G. L., and Nelson, F. R., 1973. ^{99m}Tc-polyphosphate bone imaging: a quantitative method for assessing bone healing (abs). *Journal of Nuclear Medicine, 14*, 457.

Subramanian, G., and McAfee, J. G., 1971. A new complex for skeletal imaging. *Radiology, 99*, 192–196.

Subramanian, G., McAfee, J. G., O'Mara, R. E., Rosenstreich, M., and Mehter, A., 1971. ^{99m}Tc-polyphosphate PP46: a new radiopharmaceutical for skeletal imaging (abs). *Journal of Nuclear Medicine, 12*, 399–400.

Thrall, J. H., and Geslien, G. E., 1974. Hyperaemic affects in skeletal imaging (abs). *Journal of Nuclear Medicine, 15*, 538.

Tilden, R. L., Jackson, J., Enneking, W. F., Deland, F. H., and McVey, J. T., 1973. ^{99m}Tc-polyphosphate: histological localization in human femurs by autoradiography. *Journal of Nuclear Medicine, 14*, 576–578.

Trueta, J., 1957. The normal vascular anatomy of the human femoral head during growth. *Journal of Bone and Joint Surgery, 39B*, 358–394.

Tucker, F. R., 1949. Arterial supply to the femoral head and its clinical importance. *Journal of Bone and Joint Surgery, 39B*, 82–93.

1950. The use of radioactive phosphorus in the diagnosis of avascular necrosis of the femoral head. *Journal of Bone and Joint Surgery, 32B*, 100–107.

Webber, M. M., Wagner, J., and Cragin, M. D., 1974. Femoral head blood supply demonstrated by radiotracers (abs). *Journal of Nuclear Medicine, 15*, 543.

Zimmer, A. M., Isitman, A. T., Schmitt, R. A., and Holmes, R. A., 1974. Enzymatic inhibition by diphosphonate: a proposed mechanism of tissue uptake (abs). *Journal of Nuclear Medicine, 15*, 546.

Book reviews

Dynamic Studies with Radioisotopes in Medicine 1974. Proceedings of a Symposium, Knoxville, July 15–19, 1974. Vol. I, pp. 489, illus., Vol. II, pp. 443, illus., 1975 (Vienna, International Atomic Energy Agency), £11·50 (Vol. I), £10·50 (Vol. II).

The first I.A.E.A. Symposium on this topic was held in Rotterdam in 1970, and the proceedings of the second symposium suggest that there is every promise of a series of future meetings whose importance will at least equal and possibly exceed that of the well-established symposia on medical radioisotope scintigraphy.

These volumes contain the full text of the 67 papers which were presented as well as reports of the discussions. They are classified under the headings: instrumentation and techniques; hepatic, gastrointestinal, renal and thyroid function studies; and miscellaneous dynamic studies (Vol. I). Regional blood flow, cardiac and pulmonary function studies are covered in Vol. II.

Most of the studies reported are based on the use of Anger cameras with digital data acquisition and processing systems which permit serial count-rate measurements in selected "regions of interest". It is evidently becoming an article of faith that the availability of such a system is an essential prerequisite for the study of dynamic processes in living systems. This probably accounts for the emphasis on those processes which occur in seconds or minutes. There are, however, a few papers based on *in-vitro* sample measurements on topics such as red-cell survival, protein synthesis and carbohydrate metabolism, which serve as reminders that there are longer term dynamic processes which may be of equal importance.

The participants were nominated by the national authorities of some 30 countries, which means that scientific merit was not the sole criterion governing the selection of papers. Apart from the six invited review papers, the quality ranges from the interesting and useful to the mediocre, though the former group predominate. Nevertheless, like the other I.A.E.A. symposium proceedings, this conference report is extremely valuable for those who require a synoptic view of what is actually being done in this particular field on a world wide basis, even though the choice of venue on this occasion meant that only 40 per cent of the participants represented the 29 countries other than the U.S.A.

As always, the scientific secretariat of the Agency have made an excellent job of producing the report and editing the conference discussions which represent such an important part of the proceedings. It need hardly be said that these volumes are essential for the library of any department dealing with medical radioisotope applications generally and clinical physiology in particular.

N. Veall.

Radionuclide Studies of the Spleen. By R. P. Spencer and H. A. Pearson, pp. 221, 1975 (Ohio, C.R.C. Press), $34.95.

In the preface to this monograph the authors declare that it is meant to reflect the role of the spleen in the various disorders discussed, without any attempt at a complete consideration of other aspects of the diseases.

Most common non-infectious conditions in which the spleen may be involved are mentioned, although in many cases the descriptions would be barely adequate for a medical student reading for finals, and of no interest to any post-graduate. A good deal of space is spent discussing measurement of size and volume, but the situation in which such measurements are of clinical relevance are not described. On the other hand the measurement of red cell or plasma sequestration receive only a passing reference, despite their being of considerable importance in the management of polycythaemia.

Every chapter is followed by a bibliography which is in most cases a fairly adequate review of the older literature, but less sure on more recent papers, especially those published outside the U.S.A.

The style adopted by the authors is not one commonly found in serious scientific writing, being sesquipedalian, interspersed with solecisms such as "The reason for the occurrence of splenic infarcts is likely related to the peculiarities of the circulation with the organ' [*sic*].

There is no group to whom this volume can be recommended. The review copy is in the library of The British Institute of Radiology. This should saturate the market in the United Kingdom.

M. V. Merrick.

1976, *British Journal of Radiology*, *49*, 547–549

Technical notes

A graphic display system for use with a computer-assisted tomographic scanner

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(*Received April, 1975 and in revised form September, 1975*)

A computer-assisted transverse axial tomographic scanner, made by EMI Ltd., Hayes, Middlesex, has been described by Hounsfield (1973) and clinically evaluated by Ambrose (1973) and Paxton and Ambrose (1974).

A system which uses the flexibility of a general-purpose digital computer to carry out any data manipulation found to be desirable is under development at Atkinson Morley's Hospital for the on-line or off-line display of pictures produced by this scanner. Work which would otherwise cause interruption of the scanning schedule can be transferred to the system.

The computer used is an Arcturus A18D (Arcturus Electronics Ltd., Feltham, Middlesex) which has been interfaced by the company to a 35 cm high-speed monochrome graphic display unit. The contents of a 6,400 word block of core are displayed as a matrix of 160×160 4-bit elements thus allowing 16 grey-scale levels for each element. Additionally, the interface can generate a 16 bar test-card, and also has the facility to set to Level 16 (maximum brightness) or Level 1 (minimum brightness) any particular grey-scale level. The picture is refreshed at a rate of 58 Hz, which causes some reduction of the computer processing speed. Pictures produced by the scanner are stored on industry compatible magnetic tape, and are read into the graphic display system from this medium.

PRESENT FACILITIES

Two facilities have so far been implemented using this system:

(1) A straightforward scan display direct from magnetic tape, using the "window level" and "window width" parameters (Hounsfield, 1973).
(2) An area analysis option which calculates the area, mean attenuation value, and standard deviation of attenuation value within a specified region of a scan. A bright or dark spot can be moved up, down, left or right on the screen by typing U, D, L or R at a keyboard. The spot is moved in such a way as to trace out the required region.

The figures, which are Polaroid camera pictures from the graphic display unit, illustrate the use of the unit and the present facilities.

Figure 1A shows a scan of a normal ventricular system. In Fig. 1B one grey-scale level has been set to minimum brightness so that certain features are emphasized. No information is added to the picture by this manoeuvre, but the attention of the observer is drawn to areas of similar attenuation value which may be missed at first glance. Figure 2A shows a glioma which has been enhanced by a contrast medium (sodium iothalamate) while Fig. 2B is the same scan without enhancement. Setting a grey-scale level to minimum brightness in the unenhanced scan has highlighted an area of abnormality in the region of the tumour. Figure 3 shows a right frontal meningioma, the outline of which has been traced in order to calculate the area of the tumour.

FUTURE EXTENSIONS TO THE SYSTEM

It is intended that the system will become an integral part of the methods used to display images from the EMI-Scanner at Atkinson Morley's Hospital. To this end it is proposed to have a direct link between the scanner and the graphic display system (possibly using the method described by Shields *et al.*, 1974). In this way pictures can be transferred directly to the graphic display system's discs, rather than via magnetic tape.

The following options will be added to the software available:

(1) Scan subtraction, *e.g.* scans taken with and without a contrast medium, or scans taken at different X-ray tube voltages.
(2) The production of vertical sections by taking data from a series of scans for one particular patient.

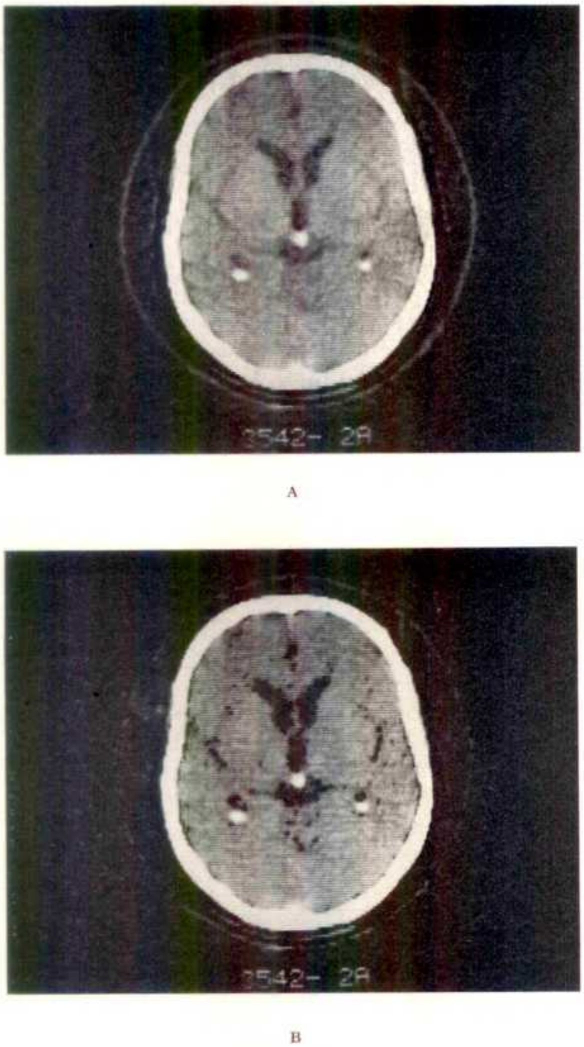

FIG. 1.

Polaroid photographs from the Graphic Display Unit: Normal ventricular system.

(A) Standard display.

(B) The effect of setting to minimum brightness one of the 16 levels of intensity in the display.

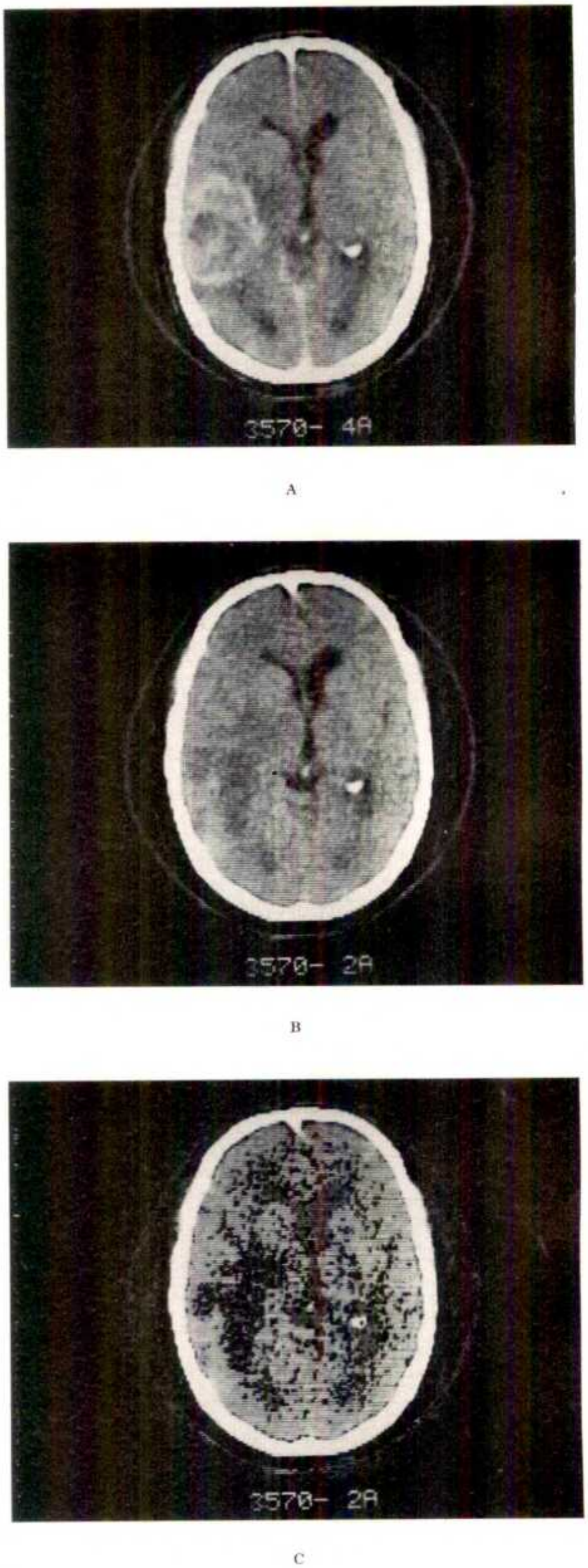

FIG. 2.

Similar photographs: Glioma.

(A) Conray enhanced.

(B) Unenhanced.

(C) One grey-scale level set to minimum brightness.

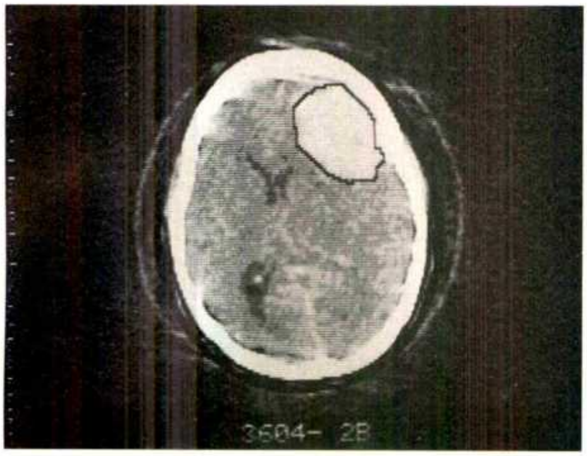

FIG. 3.

Right frontal meningioma: outlined.
Area = 1,807 mm^2
Mean attenuation value = 40·9.
Standard deviation of attenuation value = 4·2.

(3) A three-dimensional representation produced by taking data from a series of scans and reconstructing a "radiograph". The resultant picture can be viewed from certain directions with or without the effect of the skull included.

It is not to be expected that these displays will be needed for every scan, but it is likely that all will have a place in particular situations, and may show up certain factors in a clearer way than the conventional display.

ACKNOWLEDGMENTS

The authors wish to acknowledge the help they have received from the Cancer Research Campaign, who are funding this project. Acknowledgments are also due to the staff of the Radiology Department, Atkinson Morley's Hospital, the staff of Arcturus Electronics Ltd. for their generous assistance, and the Physics Department, Atkinson Morley's Hospital, especially Mr. R. Howard, for making the Polaroid camera-mount.

REFERENCES

AMBROSE, J., 1973. Computerized transverse axial scanning (tomography): Part 2. Clinical application. *British Journal of Radiology*, *46*, 1023–1047.

HOUNSFIELD, G. N., 1973. Computerized transverse axial scanning (tomography): Part 1. Description of system. *British Journal of Radiology*, *46*, 1016–1022.

PAXTON, R., and AMBROSE, J., 1974. The EMI-Scanner. A brief review of the first 650 patients. *British Journal of Radiology*, *47*, 530–565.

SHIELDS, R. A., ISHERWOOD, I., and PULLAN, B. R., 1974. The use of an off-line static display system with a computerized transverse axial tomographic unit. *British Journal of Radiology*, *47*, 893–895.

Analysis of regions of interest in EMI scans

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(*Received December 1975*)

Many authors have indicated the use of contrast material to enhance the diagnostic effectiveness of examinations by EMI-scanner. The possibilities of using the temporal sequence of the contrast accumulation as a further aid in differential diagnosis has been discussed by Hatam *et al.* (1975).

EMI supplies a diagnostic programme* in which the mean value is calculated for a rectangular region or a region of arbitrary outline but in which each row of figures must be programmed. Since most lesions are approximately elliptical and the region must be reintroduced for each picture of a series, use of this programme is difficult and time-consuming.

In order to be able to calculate the temporal changes with greater facility a programme has been designed which calculates the mean attenuation coefficient and the standard deviation of a given region. The region may be elliptical or rectangular and the orientation varied as required. The programme may be used for all pictures of a series, even with several overlapping regions assigned in each picture.

The use of the programme has shown frequent slight changes of position of the patient's head in all planes, thus adequate fixation of the head is a necessary prerequisite for a refined regional analysis.

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*Operating instruction for magnetic tape diagnostics. EMI Instructions.

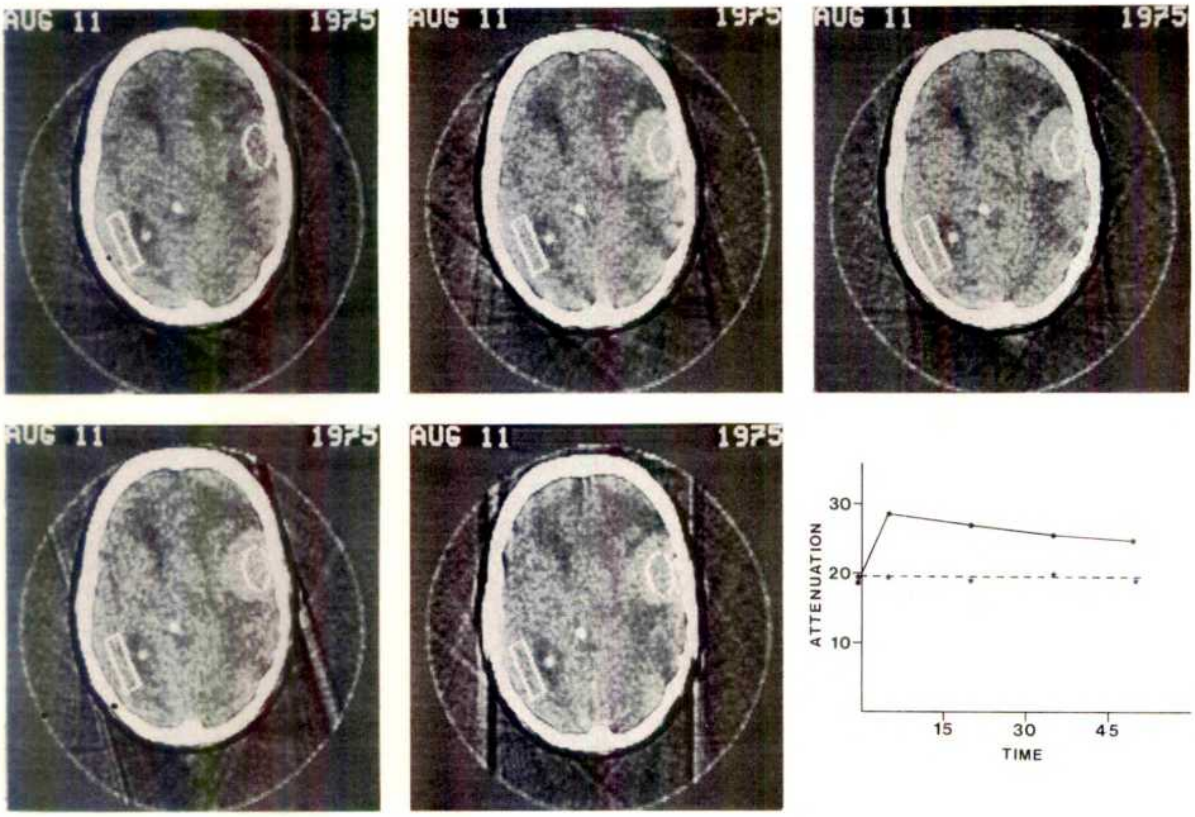

Fig. 1.

Scans of the same section of a patient with a right-sided meningioma taken before and 5, 20, 35 and 49 minutes after a bolus injection of contrast material. The graph shows the temporal changes of mean EMI-number in the outlined regions.

However, correction of movements in the plane of the tomograph has been achieved by assessing changes in the position of the skull, and automatically moving the region of interest to conform with these changes. Attempts to correct for transpositioning of the centre of gravity met with difficulty because it was too sensitive to movements out of plane.

The programme is employed by transferring the sections in question from storage tape to a disc containing the programme. Following calculation of the values of the region, the sections with the regions outlined may be transferred back to tape and displayed.

The programme is written in FORTRAN and runs on the Nova 820 with the EMI-scanner using a RDOS system.

Acknowledgments

This work was supported by a grant from Riksföreningen mot Cancer (Swedish Cancer Society).

REFERENCE

Hatam, A., Bergvall, U., Lewander, R., Larsson, S., and Lind, M., 1975. Contrast medium enhancement with time in computer tomography. *Acta Radiologica, Supplement No. 346*, 63–81.

1976, *British Journal of Radiology*, *49*, 551–554 JUNE 1976

Technical notes

The treatment of ophthalmic tumours with low-energy sources

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(*Received October 1974 and in revised form September 1975*).

One of the features which detract from the advantages of insertion or implantation of radioactive sources in the treatment of tumours is the difficulty in screening sensitive structures within the treatment volume.

In addition, where very large doses are administered with electro-magnetic radiation, for instance in the treatment of intra-ocular tumours with radioactive plaques, the doses administered to surrounding structures may be considerable. It seems that these difficulties might be largely overcome by the use of low-energy isotope sources and suitable integral shielding.

For example, the use of ^{125}I seeds has been considered, which were first described by Henschke and Lawrence (1965). The isotope emits 27 to 35 keV X rays which permit highly effective screening by thin lead foil (0·25 mm of lead reduces primary radiation from ^{125}I by 99·9 per cent, and absorbs scattered radiation and secondary electrons almost entirely). Suitable seeds for this purpose, consisting of radioactive sodium iodide absorbed onto ceramic beads, may be obtained from the Lawrence Soft Ray Corporation, California. Each titanium-encapsulated seed contains two such beads separated by a radio-opaque gold marker. The seeds are 4·5 mm long and 0·75 mm in diameter. Seeds of 4 mCi activity are now available, which are suitable for the building of applicators and, after a reasonable period of decay, for implantation. Their repeated use makes treatment with this isotope relatively cheap.

The high linear attenuation coefficient of about 0·035 cm^{-1} in tissue and easy screening makes the handling and nursing of patients with these sources *in situ* remarkably simple.

The principle of integral shielding can be applied to three distinct treatment situations in the eye. Firstly, the eyelids alone; secondly, the eyelids and the conjunctiva; and thirdly, treatment of the global contents. Three cases are described, illustrating the principle in each of the three situations.

CASE REPORTS

Case 1

A Caucasian female aged 75 years presented complaining of a swelling of the outer portion of the upper eyelid for 12 months. This was painless, progressive, and measured about 8 mm in diameter.

A biopsy showed a mucin-secreting adenocarcinoma to be present, and it was considered that this tumour arose from meibomiam glands. The patient was admitted to hospital and it was elected to treat her by means of ^{125}I seed implants.

Protection of the cornea and lens was achieved by suturing a protective Teflon-coated brass shield, 0·3 mm in thickness, over the anterior aspect of the globe (now replaced by stainless steel). The shield was 22 mm in diameter and consisted of two parts (Fig. 1): the outer ring which rested on the globar conjuctiva and a window which was 12 mm in diameter. The window is occluded by a domed plate which clears the cornea by 1 mm. Perforations are present in the brass ring to allow for suturing to the sclera and for the passage of tears. Similar perforations allow the passage of tears through the domed plate and also allow it to be seized with forceps for removal and inspection of the cornea. If necessary, this can be done daily.

After the insertion of the ring and domed plate, the implant can be performed. Polythene tubing 1·5 mm in external diameter, is loaded with ^{125}I seeds, threaded upon a large needle, and sutured into the base of the upper and lower lids in a crescentic fashion. The suturing is made easier by a needle with screw end, rather than an eye, the screw being inserted into the polythene tubing. In this case, six seeds of 0·63 mCi activity each were used in the upper and lower tubing respectively. In addition, five seeds were inserted into tubing which was sutured to the free margin of the upper lid and two tubes, each containing two seeds, were inserted into the tumour itself. The tubing emerged at each end and was passed through a Perspex washer, 3 mm in diameter, and kept in place by a 3 mm diameter lead washer which was crimped with a pair of pliers. A radiograph of the implant is shown (Fig. 2).

The computed dose through the centre of the base of the tumour was 5,000 rad in 264 hours.

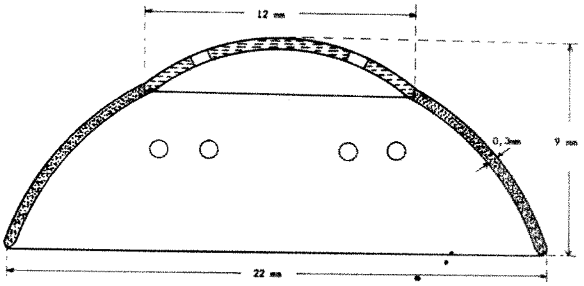


FIG. 1.

Protective shield for the cornea and lens as used in Case 1.

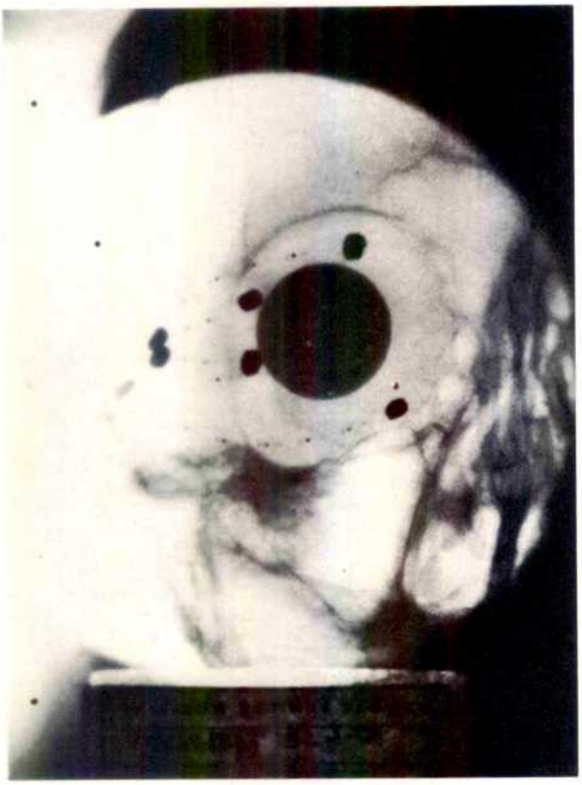


Fig. 2.
Radiograph of the implant in Case 1.

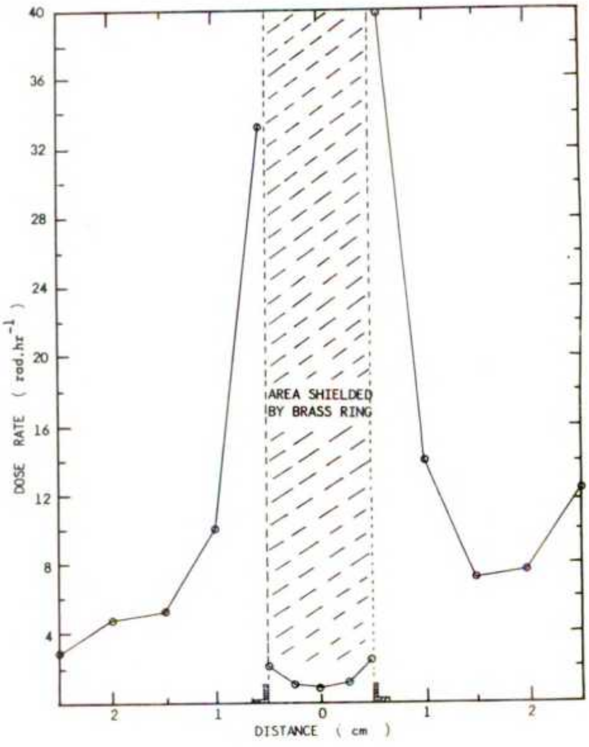


Fig. 4.
Computed dose distribution along the line AB in Fig. 3.

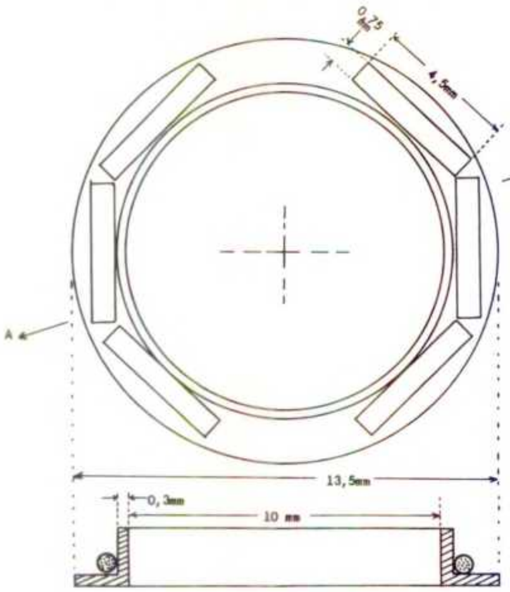


Fig. 3.
Brass ring with six sources along the line of the limbus as used in Case 2. Brass is represented by the hatched area in the cross-section shown below the plan view. The plastic conjunctival shield is not shown.

Case 2

The patient, a 69-year-old Caucasian female, had had a story of black spots on the bulbar and palpebral conjunctiva for 20 years. On four previous occasions, black tumours had been excised from the eye, at least three of which were malignant melanomata.

When first seen in the Ocular Tumour Clinic, there were pigmented masses on the globar conjunctiva medially and laterally, the latter extending onto the lower lid. The outer canthus was shortened by previous surgery. Biopsy of the masses again confirmed the presence of a malignant melanoma. A diagnosis of melanosis of the tarsal and bulbar conjunctiva with diffuse malignant change was made.

The bases of the upper and lower eyelids were implanted with the same technique as used in Case 1. The irradiation of the conjunctival sac was effected by the insertion of a plastic applicator which contained a brass ring (Fig. 3). Six sources of 0·65 mCi activity each were mounted on the outer aspect of the ring. The ring followed the line of the limbus and screened the lens from the sources placed on its outer aspect. The patient was able to wear this applicator for a week with no undue discomfort and no complications. A computed dose distribution is shown across the line AB in the plane of the implant passing through the centre of the brass ring, parallel to the long axis of the eye (Fig. 4). Any possible effect of secondary electrons from the ring was ignored because the ring was embedded into a plastic applicator.

The irregular dose-rate shown is due to the discontinuous and asymmetrical distribution of the sources in the implant relative to the measured diameter. An average computed dose of 1,750 rad was delivered in 166 hours. This average value was calculated along a line 5 cm long passing through the centre of the ring with extreme values of 950 and 2,700 rad at the ends, ignoring the low dose-rates inside the ring. (A radiograph of the completed configuration is shown in Fig. 5.) There was total regression of the malignant melanoma six months after treatment, and no evidence of damage to the cornea or the lens of the eye.

Case 3

A 66-year-old Caucasian male presented to the Ocular Tumour Clinic complaining of a shadow which he had seen superolaterally in the right visual field for some months. This appeared to be enlarging.

Examination of the fundus showed a large black mass immediately behind the iris and indenting the lens. It extended from about 2 o'clock to 6 o'clock and extended in a posterior direction for approximately 8 mm. A diagnosis of malignant melanoma of the choroid was made. Systemic examination and investigation showed no evidence of spread of the disease. The patient refused enucleation and it was therefore decided to treat the lesion by means of a directional low-energy applicator.

The applicator was semi-circular in outline and made to extend halfway around the limbus. It extended posteriorly from the limbus for 14 mm. Fourteen ^{125}I seeds of 0·56 mCi activity were used. The applicator was covered by a lead foil, 0·5 mm thickness, which extended over the sources placed along the limbus and extended vertically down to the limbus. This conferred a directional effect on the applicator and screened the lens of the eye and cornea. (Any possible effect from secondary electrons from the lead was ignored since their energies would be low and absorbed in the plastic retaining the seeds in the applicator.) The doses at various points are shown in Fig. 6. It will be seen that the screened edge offered significant protection of the lens.

At operation, the conjunctiva was incised around the limbus, the medial and inferior rectus muscles were freed from the globe and the applicator sutured in place. The muscles were re-sutured temporarily to the applicator and the globar conjunctiva, as far as possible, was closed. The applicator remained *in situ* for eight days and delivered a dose of 3,600 rad to the apex of the lesion. It was then removed, the muscles re-attached and the conjunctiva re-sutured.

Six weeks after the removal of the applicator, examination showed the patient to be in excellent condition, with no complaints. There had been dramatic regression of the tumour (which was apparently continuing) and all that could be observed through the dilated pupil was a small residual knuckle of dark tumour at 4 o'clock.

Screened applicators may also be used in treating other lesions in other sites within the globe of the eye. It is possible to introduce suitable screening to protect the optic nerve, should this be adjacent to the tumour and thus avoid the danger of optic neuritis, which may be seen following the use of penetrating gamma rays. The bones of the orbit may also be protected.

Measured dose distributions, using a small solid-state detector, indicated that the relative depth doses obtained with ^{125}I compared well with those obtained using ^{182}Ta and ^{60}Co sources, and that very effective edge screening was obtained using the thin brass ring in conjunction with ^{125}I sources.

Discussion

The use of ^{125}I or other similar low-energy-producing isotopes with integral shielding of implants and applicators appears to be a new departure in the treatment of ophthalmic tumours. A highly attractive flexible system is provided, whilst at the same time total shielding of the sensitive structures in the globe and elsewhere is allowed. This would appear to confer a distinct advantage upon the implantation techniques previously reported by Lederman (1956) for melanosis occuli, and the ^{60}Co applicators reported by Stallard (1955) for the treatment of retinoblastoma and malignant melanoma of the choroid. The small seeds used lend themselves to both implantation in polythene tubing and to the construction of suitable applicators.

The good regression seen in Cases 2 and 3 of malignant melanoma, with relatively small doses, might suggest that the RBE is greater than 1. More

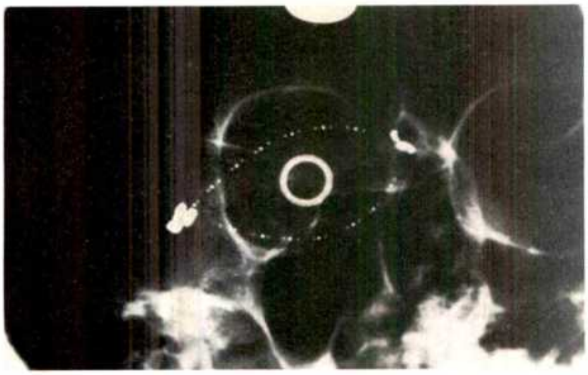
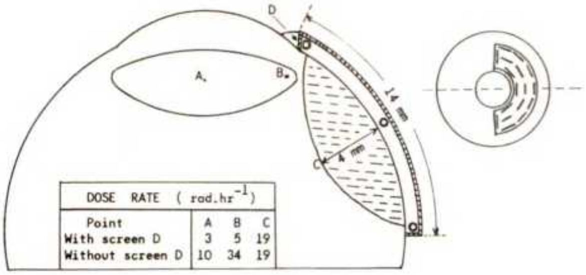


Fig. 5.

Radiograph of the completed configuration (Case 2).



DOSE RATE (rad.hr^{-1})			
Point	A	B	C
With screen D	3	5	19
Without screen D	10	34	19

Fig. 6.

Sectional view of eye, tumour and directional applicator in Case 3. Dose-rate at points A, B and C are shown in the table.

information in this area is being acquired at the present time.

The low absorbed dose used in Case 2 was dictated by the activity of the sources available and the original intention was to repeat the application. This however, has not proved necessary.

ACKNOWLEDGEMENTS

Thanks are due to Dr. J. G. Burger, Medical Superintendent, Groote Schuur Hospital, for permission to publish. We would like to record our thanks to Mr. W. Kay and Mr. D. W. Stuart of the Medical Physics Workshops, and Mr. E. A. J. Buret and Mr. H. Cleminshaw of the Radiotherapy Mould Room, without whose participation this work would not have been possible.

REFERENCES

HENSCHKE, U. K., and LAWRENCE, D. C., 1965. Cesium-131 seeds for permanent implants. *Radiology 85*, 1117–1119.

LEDERMAN, M., and SINCLAIR, W. K., 1956. *Radioactive isotopes for beta and gamma ray applicators in Therapeutic use of artificial radioisotopes.* Edited by P. F. Hahn, pp. 344–364 (J. Wiley, New York).

STALLARD, H. B., 1955. Multiple islands of retinoblastoma. Incidence rate and time span of appearance. *British Journal of Ophthalmology, 39*, 241–243.

Book reviews

Atlas of the Battered Child Syndrome. By J. M. Cameron and L. J. Ray, pp. ix+90, illus. in colour, 1975, £8·50.

This book achieves its stated aim to help in distinguishing accidental injury from the injuries found in the battered child on clinical and X-ray examination.

While the early part of the book does not give great prominence to the important role played by radiologists, notably John Caffey, in the description and identification of this condition, this is more than compensated by the excellent section on radiographic findings and differential diagnosis, which accounts for just over half the total subject-matter in the book. The fact that skull injuries on their own are usually not enough to confirm a suspicion of battering is noted, and also the appearances of some of the accessory sutures which may be confused with vault fractures are described. Due prominence is given to the type of metaphyseal injury seen in the long bones and characteristic of the battered child. These lesions are well described and the illustrations are of good quality. The difficulty which may be experienced in identifying rib fractures in radiographs of young infants is exemplified by the fact that many of the radiographs are of post-mortem specimens without the overlying lung and mediastinal shadows.

When the radiologist is confronted with the possibility of a battered baby, the questions which commonly arise relate to the possibility of the bones being intrinsically weak, due to some underlying condition such as osteogenesis imperfecta, the need to know approximately how long before the examination the injury is likely to have been sustained and whether several injuries could all have been sustained on the same occasion. Dr. Ray points out that the actual age of a fracture may be difficult to determine without considerable personal experience, but gives a helpful timetable. There is also a very useful section on the differential diagnosis between conditions such as osteogenesis imperfecta, scurvy and the fractures found in children with paralysed limbs.

This book should be read by all trainee radiologists who may one day be called on to report radiographs of children from accident and emergency departments, and will also prove of interest to many more experienced radiologists, particularly when they are confronted with the need to give evidence in a case of suspected battering.

R. K. LEVICK.

Diagnostic Ultrasound. By M. Hussey, pp. 254, 1975 (London, Blackie), £10·50.

This book, which has been written for clinical specialists and recently-graduated scientists, represents an attempt to collect and synthesize the vast literature on the interaction of ultrasound with biological tissue and its components. After a brief introductory chapter the author provides two basic chapters: the first is on the physical principles of ultrasound and the second is a 24-page summary of the physical structure of matter, thermodynamics, chemical dynamics, cell structure and function and tissue types. The range of physics presented is greater than is usually found in texts on medical ultrasonics, but its relevance to the question under discussion is not always clearly shown.

The heart of the book lies in the four chapters describing the literature on the interaction of ultrasound with: water and aqueous solutions of small molecules, biological macromolecules in solution, cells and subcellular particles, and tissues and organs respectively. The quality of the text ranges from a succession of abstracts to perspective synthesis. As a whole it lacks both formative criticism and crystalline summaries. The reader should also note that the data of Goldman and Hueter (1957) in chapter 7 appears to be represented inaccurately, some paragraphs being spent in discussing the scientific reasons behind the difference of this and later work.

The penultimate chapter on dosimetry suffers from three fundamental shortcomings. Firstly (following the discussion in Chapter 2), attenuation and absorption are assumed to be the same; secondly, the discussion would have been greatly clarified by the use of the word "exposure", and thirdly, little comment is made upon the present achievements and limitations of methods of measurement of exposure and dose. This last is surprising in view of the fact that these concepts must underpin the whole volume. The book is concluded with a summary chapter on safety aspects of diagnostic ultrasound.

One aspect of synthesis is that its achievement emphasizes the areas of uncertainty. To this extent the aim has not been achieved—perhaps because of the very broad base of the book and the state of present knowledge. In spite of its shortcomings the volume will probably be a convenient, if not always reliable, source of reference.

R. C. CHIVERS.

1976, *British Journal of Radiology*, *49*, 555–556

Case report

Primary costal echinococcosis with spine involvement

By A. Monajati, M. Zarrabi, and M. Shaffi, M.Phil., F.R.A.C.S.

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(*Received, July 1975 and in revised form February 1976*).

Reported primary hydatid disease of the rib is extremely rare and only 38 cases have been reported in the literature (Bonakdarpour *et al.*, 1973). When it presents with cord compression signs, it becomes a diagnostic dilemma.

Case history

A 32-year-old female from a rural region presented with progressive paraplegia of a month's duration. There was some muscle atrophy, decreased tone and power, and normal reflexes of the lower limbs. Radiological examination showed an extrapleural soft-tissue mass in the left upper posterior hemithorax associated with rib destruction, cystic changes in the remaining posterior segment of the rib, erosion of the lateral aspect of the corresponding vertebral body (Fig. 1), and extradural block (Fig. 2). Operative and pathological findings revealed hydatid disease of the 4th rib with an abscess in the paravertebral extrapleural space and erosion of the body and pedicle of T4. Extension into the spinal canal produced extradural cord compression. Following surgical intervention, the patient recovered.

DISCUSSION

The reported incidence of osseous hydatid disease varies between 1 per cent (Alldred and Nisbet, 1964)

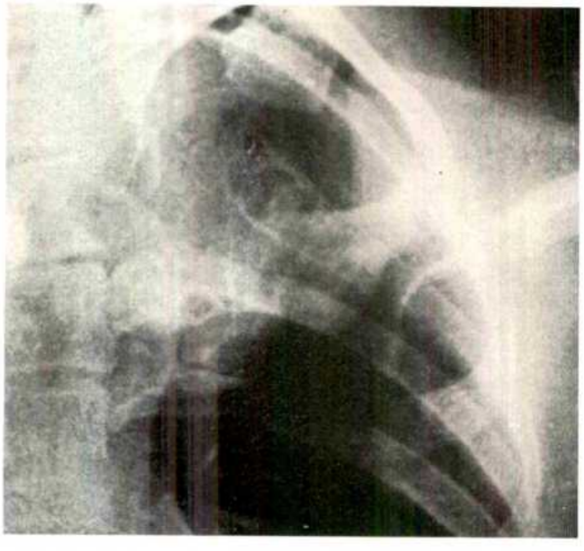

FIG. 1.

Shows cystic changes in the remaining posterior segment of the left 4th rib and erosion of the corresponding vertebra.

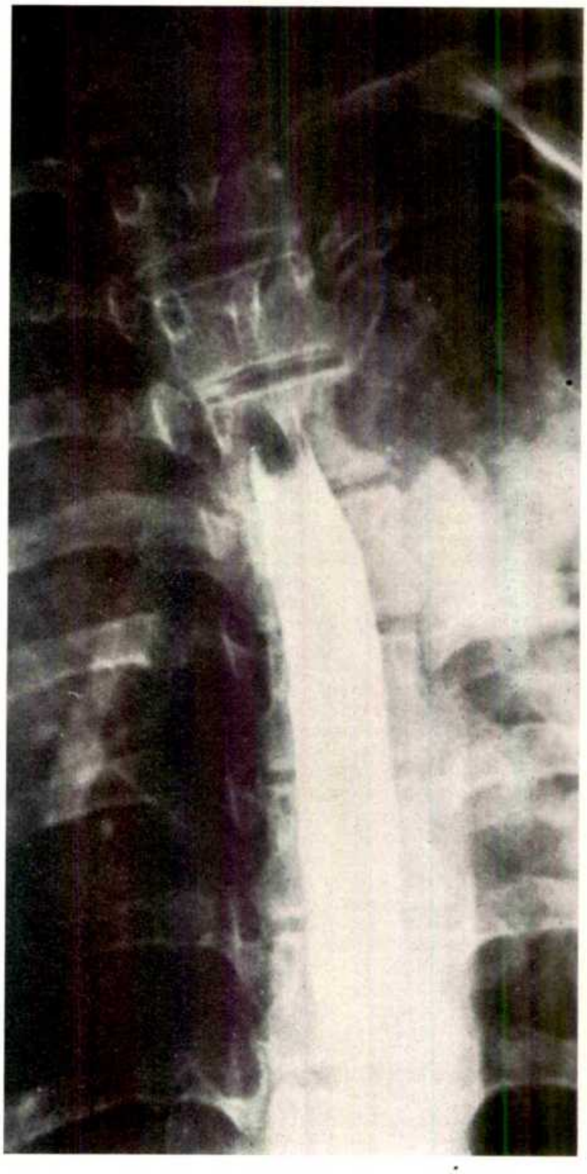

FIG. 2.

Myelogram reveals extradural block at the level of the involved vertebra.

and 2 per cent (Barnett, 1945). Rib involvement in osseous hydatid disease is extremely rare, and has been recorded in five of 243 cysts in Bauers' table (Hosemann *et al.*, 1928) and in four of 852 cysts (Felkl and Baerwolff, 1958). Most cases are reported as spinal lesions because patients usually do not seek medical advice until neurologic symptoms develop (L'Agrot *et al.*, 1969; Murray and Haddad, 1959). The cyst is usually located in the posterior portion of the rib and presents radiologically as a multiloculated osteolytic lesion in the rib, sometimes with a sclerotic margin. The lesion slowly grows to involve vertebrae or adjacent soft tissues. If the lesion breaks through the cortical portion of the rib, it will produce an extrapleural soft tissue mass or abscess. In the more advanced stages, the lesion not only involves the vertebra, but may also extend into the spinal canal and cause cord compression as in our case.

REFERENCES

Alldred, A. J., and Nisbet, N. W., 1964. Hydatid disease of bone in Australasia. *Journal of Bone and Joint Surgery*, *46*, 260.

Barnett, L. E., 1945. Hydatid registry. *Australian and New Zealand Journal of Surgery*, *15*, 72.

Bonakdarpour, A., Alizadeh, Y. F., Maghssoudi, H., Shariat, S., and Levy, W., 1973. Costal echinococcosis. *American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine*, *118*, 371–376.

Felkl, K., and Baerwolff, G., 1958. Zur klinischen Problematik der Knochenechinokokkose. *Chirurg*, *29*, 207.

Hosemann, G. R., Schwartz, J. C., and Lehmann, A., 1928. Posselt: Die Echinokokkenkrankheit. *Neue Deutsche Chirurgie*, *40*, (F. Enke, Stuttgart).

L'Agrot, F., Costagliola, M., Micheau, P. H., Migueres, J., and Jover, A., 1969. L'echinococcose costale: forme rare d'echinococcose osseuse. *Annales de Chirurgie*, *23–C*, 607–614.

Murray, R. O., and Haddad, F., 1959. Hydatid disease of spine, *Journal of Bone and Joint Surgery*, *41–B*, 499–506.

Book reviews

Cell Survival after Low Doses of Radiation: Theoretical and Clinical Implications. Edited by Tikvah Alper (Proceedings of the L. H. Gray Conference, September 1974), pp. 397, 1975 (John Wiley & Sons Ltd.), £13·50.

Here is a book that will become necessary reading for advanced students of radiobiology. It is a full record of the 6th L. H. Gray Conference with the contributed papers, skilfully edited discussion and a useful summary. The editor and her collaborators are to be congratulated for producing this volume so quickly after the Conference while the ideas are still warm.

The Conference was set a series of questions concerning the theory, measurement and relevance to radiotherapy of survival curve shoulders and most of the papers are relevant to this theme. The early sections are largely about *in vitro* studies and there are a number of critically constructive papers on the design and statistical analysis of experiments aimed to investigate the low-dose survival region. For those so inclined a number of survival curve theories are presented but the experimental points can be fitted to most of them so that one's choice of theory must depend on faith. The continuing rearguard skirmishes about recovery effcts at very low oxygen levels are chronicled but their relevance must remain doubtful until we have a more precise picture of oxygen levels *in vivo* during a course of irradiations.

Later sections of the book describe the ingenious methods that have been devised for normal and tumour tissues to measure the ratio of initial to final slopes of survival curves for cells irradiated *in vivo*. The merits of the various approaches are compared and although the fractionation models are coming closer to radiotherapy practice the measurements of shoulder parameters still lack the precision to be of predictive value.

This book will set the fashion for cellular *in vitro* and *in vivo* radiobiology for some time to come. Indeed, the parallel with fashion is close since it is evident that following the example set here shoulders will be exposed and worn much lower than before.

N. F. Kember.

Computer Processing of Dynamic Images. pp. iv + 211, 1974 (Medical and Technical Publishing Co. Ltd.), £7·00.

This book contains the proceedings of a workshop on the use of gamma-camera computer systems in dynamic radioactive tracer studies. The workshop was held in 1971 in St. Louis, Missouri, and the proceedings were published in 1974.

The book starts with a number of chapters devoted to aspects of camera function and performance, the computer, and its interface to the camera and software. The subject matter is dealt with adequately but is limited by the state of development of cameras and computers available prior to 1971; more recent developments are not included. The basic principles do, however, still apply and are in general clearly explained by the authors of the chapters covering this subject matter. The book goes on to deal with mathematical models for interpreting dynamic tracer data and in this section covers the physical principles of tracer kinetics together with mathematical and statistical methods for analysing data. This part of the book is written by well-known authors and is worth reading by both students and workers in the field who have some mathematical ability. The last section of the book is concerned with the clinical implications of dynamic imaging technology and consists of a series of summaries of panel discussions which dealt with the brain, lung and kidney. It is unfortunate that the heart was not included. This last part of the book will probably be of interest to those who attended the workshop but is too disjointed and out of date to be of much help to people who are working in the field at this time.

In summary, therefore, the book is worth reading by those who wish to gain a grasp of the basic physics, engineering and mathematical principles of computer processing of dynamic images but would be of little value to those with a purely medical interest in the applications of the technology.

B. R. Pullan.

1976, *British Journal of Radiology*, *49*, 557

Proceedings of The British Institute of Radiology

Xeroradiography: some new applications*

Abstracts of papers read at a meeting held in the Reid-Knox Hall, Institute House, 32 Welbeck Street, London W1M 7PG, on Thursday, October 16, 1975

Xeroradiography in dentistry, by W. H. Binnie, R. A. Cawson, A. J. Stacey and R. Davis
Clinical applications of xeroradiography, by I. H. Gravelle

XERORADIOGRAPHY IN DENTISTRY

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The first xeroradiograph of dental application was reported by Hills *et al.* in 1955. This was a lateral oblique jaw projection but the exposure needed was unacceptably high. James *et al.* (1973), however, showed that by increasing the kilovoltage to 120 the exposure could be reduced by 60 per cent. Using this higher kV we have produced lateral oblique jaw and lateral skull xeroradiographs with a lower incident skin exposure than conventional radiographs (Binnie *et al.*, 1975). Bony and dental structures are much more sharply defined on xeroradiographs, and soft tissues are visible on the same picture without use of a grid or wedge filter. These features are of great advantage in cephalometrics and cosmetic maxillo-facial surgery.

Panoramic xeroradiographs are potentially the most useful application of the xeroradiographic principle to dentistry. The combination of full jaw coverage with the sharp definition only possible at present from intra-oral radiographs would be of benefit to the dentist, save time for the radiographer and reduce the dose to the patient. Excellent results have been obtained with post-mortem specimens at 90 kV but optimal exposure for a normal adult requires a panoramic X-ray machine giving about 120 kV.

REFERENCES

BINNIE, W. H., STACEY, A. J., DAVIS, R., and CAWSON, R. A., 1975. Applications of xeroradiography in dentistry. *Journal of Dentistry*, *3*, 99–104.

HILLS, T. H., STANFORD, R. W., and MOORE, R. D., 1955. Xeroradiography II. The present medical applications. *British Journal of Radiology*, *28*, 545–551.

JAMES, P., BADDERLEY, H., BOAG, J. W., JOHNS, H. E. and STACEY, A. J. 1973. Xeroradiography – its use in peripheral contrast medium angiography. *Clinical Radiology*, *24*, 67–71.

CLINICAL APPLICATIONS OF XERORADIOGRAPHY

By I. H. Gravelle
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Xeroradiographic images have a relatively low broad contrast but a high local contrast at the edges of tissues of different densities. The margins of lesions and normal tissues are accentuated. Densities are more easily penetrated and there is a wide recording latitude.

The technique is at its best when used in soft-tissue radiography where the boundaries between the various tissues are highlighted. This applies to soft-tissue examinations of all kinds but in particular to breast radiography and especially in the examination of dense dysplastic breasts. Microcalcifications in such cases are accentuated.

An ability to penetrate dense areas is of value in mediastinal tumours, pleural effusions and lung tumours. The wide recording latitude is useful in radiography of the neck, mediastinal and pulmonary tomography and also in the demonstration of the alignment of fractures in plaster casts.

Tomography of the larynx, sinuses and joints is possible and a wide variety of contrast examinations may be carried out using less concentrated opaque media.

Radiation dosage is less in xeromammography than in film mammography and the dosage in xeroradiography of the extremities is comparable with that obtained with non-screen, film techniques. However, when a film-screen combination is employed, then the dosage is always less for this combination than for the equivalent xeroragraphic examination.

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1976, *British Journal of Radiology*, *49*, 558–561

Proceedings of The British Institute of Radiology

Abstracts of papers read at the Radiobiology Work-in-Progress meeting held on Friday, January 16, 1976 in the Reid-Knox Hall, Institute House, 32 Welbeck Street, London W1M 7PG*

The effects of varied numbers of dose fractions and overall treatment time on the radiation response of normal human skin, by C. M. A. Young, D. Brennan, K. Durrant, J. W. Hopewell and G. Wiernik.
An *in vitro* colony assay for human tumours: radiation survival in a pancreatic tumour xenograft, by V. Doreen Courtenay and Judith Mills.
Studies on the radiosensitivity of human bone marrow and human tumour xenografts using an agar diffusion chamber technique for assaying clonogenic cells, by I. E. Smith and Myrtle Gordon.
The response of tumours to X rays and Ro–07–0582, by R. H. Thomlinson, S. Dische, A. Gray and Lesley Errington.
The effect of irradiation on normal human rectum, by D. J. D. Perrins.
The effects of radiation on the skin blood pulse, by G. D. Zanelli.
Some measurements with skin and lymphocytes, by A. H. W. Nias.
A patient with ataxia-telangiectasia showing abnormal radiosensitivity to normal doses of irradiation, by Jillian R. Mann.
Ataxia telangiectasia, radiosensitivity at the cellular and molecular level, by C. F. Arlett, A. R. Lehmann, P. H. M. Lohman and M. C. Paterson.
The radiosensitivity at the chromosomal level of lymphocytes from patients with ataxia telangiectasis, by A. M. R. Taylor, J. A. Metcalfe, J. M. Oxford and D. G. Harnden.

THE EFFECTS OF VARIED NUMBERS OF DOSE FRACTIONS AND OVERALL TREATMENT TIME ON THE RADIATION RESPONSE OF NORMAL HUMAN SKIN

By C. M. A. Young, D. Brennan, K. Durrant, J. W. Hopewell and G. Wiernik

Research Institute, Churchill Hospital, Headington, Oxford

The early and late radiation response of small areas of normal human skin, included in the treatment of basal cell carcinomata, have been evaluated for treatment given over a range of dose fractions (3, 7, and 10 fractions) with the overall treatment time constant (14 days). A further study in which time has been varied (4, 10 and 28 days) for a fixed number of fractions (5 fractions) is in progress.

For areas treated over a constant time period (14 days) the pattern of increasing and declining early skin reaction and the proportion of treated fields reaching skin tolerance were similar for the three fractionation groups. The same was true of the late tissue damage.

Of particular interest was the observation that the final cosmetic result and tumour cure was not significantly improved by treatment given as 10 fractions over that obtained with three fractions, both given in 14 days.

AN "IN VITRO" COLONY ASSAY FOR HUMAN TUMOURS: RADIATION SURVIVAL IN A PANCREATIC TUMOUR XENOGRAFT

By V. Doreen Courtenay and Judith Mills

Institute of Cancer Research, Belmont, Sutton, Surrey

A new *in vitro* colony technique is described which has been used to measure cell survival in human tumours grown as xenografts in the immune suppressed CBA mouse. The essential features of the culture technique are the use of a reduced oxygen concentration in the gas phase and the addition of washed rat red blood cells to a single-cell suspension of the tumour cells in Ham's F12 medium with 15 per cent calf serum. These are set up in soft agar in polystyrene test-tubes gassed with 5 per cent oxygen, 90 per cent nitrogen and 5 per cent carbon dioxide before sealing. Provision is made for changing the medium to replace nutrients and remove toxic products.

Dose-response curves are presented for a pancreatic tumour exposed to γ radiation from a Co^{60} source. For tumours, irradiated *in situ*, in air-breathing or nitrogen-asphyxiated mice, and removed for assay immediately after irradiation, parallel curves were obtained with $D_0 = 300$ rad. From the displacement of the curve, an hypoxic fraction of 0·25 was calculated for the tumours in air-breathing mice.

For tumours left *in situ* for 18 hours in air-breathing animals the D_0 value was unchanged but survival was higher by a factor of 2·4. This could be due to the repair of potentially lethal damage by cells in the tumour, but not in single-cell suspension.

The survival of fully oxygenated cells was measured in a suspension irradiated *in vitro* and the value $D_0 = 90$ rad was obtained giving an oxygen enhancement ratio of 3·3.

STUDIES ON THE RADIOSENSITIVITY OF HUMAN BONE MARROW AND HUMAN TUMOUR XENOGRAFTS USING AN AGAR DIFFUSION CHAMBER TECHNIQUE FOR ASSAYING CLONOGENIC CELLS

By I. E. Smith and Myrtle Gordon

The Department of Biophysics, Institute of Cancer Research Sutton, Surrey

A technique using agar diffusion chambers has been developed for growing colonies from human bone-marrow cells (Gordon *et al.*, 1975) and, more recently, from cell suspensions of human tumours propagated in immune-suppressed mice (xenografts). Modified diffusion chambers (Gordon, 1974), loaded with cells in agar-medium, are incubated in the peritoneal cavity of pre-irradiated mice and provide standard culture conditions for the study of colony-forming cells and the effects on these of ^{60}Cobalt γ-irradiation under well oxygenated and hypoxic conditions.

The technique, in conjunction with a similar *in vitro* method (Courtenay and Hills, 1976), has been used to show a hypoxic fraction of about 0·25 in a human pancreatic tumour xenograft treated *in vivo* in an air-breathing mouse. *In vitro* radiosensitivities of two human tumour xenografts, a pancreatic carcinoma (D_0 90 rad) and a melanoma (D_0 150 rad), have been compared with that of human bone marrow (D_0 85 rad). These findings suggest that the technique may have value in treatment planning and in predicting clinical response both to radiotherapy and to chemotherapy for which the method is also being used.

REFERENCES

Courtenay, V. D., and Mills, J., 1976. An *in vitro* colony assay for human tumour xenografts. Abstract of B.I.R. work-in progress meeting, January 16, 1976. *British Journal of Radiology 49*, 558.

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*Reprints available from the Editorial Office, 32 Welbeck Street, London W1M 7PG.

Gordon, M. Y., 1974. Quantitation of haemopoietic cells from normal and leukaemic RFM mice using an *in vivo* colony assay. *British Journal of Cancer*, *30*, 421.

Gordon, M. Y., Blackett, N. M., and Douglas, I. D. C., 1975. Colony formation by human haemopoietic precursor cells cultured in semi-solid agar in diffusion chambers. *British Journal of Haematology*, *31*, 103.

THE RESPONSE OF TUMOURS TO X RAYS AND RO–07–0582

By R. H. Thomlinson, S. Dische, A. Gray and Lesley Errington

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Northwood, Middlesex

When a new régime of cancer therapy based on the effect of ionizing radiations is to be tested clinically, the response of both the neoplastic and the normal tissues included in the radiated volume must be assessed before final conclusions can be drawn. This paper is concerned with the response of tumours, that of normal tissues being described elsewhere (Dische *et al.*, 1976, Gray *et al.*, 1976).

The responses of tumours to irradiation fall into two categories; those that depend on the cells that are killed, and those that depend on cells that survive. The former class, of which regression is the classical example, is an insensitive indicator of the relative effectiveness of any two forms of treatment. Poor forms of radiotherapy are likely to kill 99 per cent of the clonogenic cells of a tumour and differences of regression are unlikely to reveal differences in the killing of the remaining 1 per cent.

The response of tumours which depends on the cells that survive is the capacity for regrowth. In experimental tumours in animals this can be tested in fresh environments, *in vitro* or *in vivo*. In human tumours regrowth can, in general, only be observed from cells left *in situ*. The timing of regrowth depends on the growth rate of the tumour and varies from one to another. The simplest means of ensuring similarity of tumours is to treat multiple metastases in the same patient, which in certain circumstances is ethically permissible.

When testing the effectiveness of a new sensitizing agent such as Ro–07–0582, most information can be gained from the comparison of doses of radiation given with and without the drug which produce the same biological effect. However, since no two effects can be shown to be identical, the comparison of a dose of radiation given with the drug must be made with at least two different doses given without. Results can only be obtained in favourable circumstances. In one patient in whom 21 nodules of subcutaneous metastases of carcinoma of the cervix were measured, two groups of seven were treated with single doses of 960 rad and 1,120 rad without the addition of the sensitizer and one group of seven was given 800 rad four hours after the oral administration of 4 g of Ro–07–0582. The results indicate an enhancement of the radiation dose by a factor of 1·2 with an approximate range of standard error from 1·1 to 1·45 (Thomlinson *et al.*, 1976).

Tests were made in several other patients, but for reasons which are discussed no conclusive results were obtained.

REFERENCES

Dische, S., Gray, A. J., and Zanelli, G. D., 1976. Clinical testing of the radiosensitizer Ro–07–0582. 2. Radiosensitization of normal and hypoxic skin. *Clinical Radiology* (in press).

Gray, A. J., Dische, S., Adams, G. E., Flockhart, I. R., and Foster, J. L., 1976. Clinical testing of the radiosensitizer Ro–07–0582. 1. Dose tolerance serum and tumour concentrations. *Clinical Radiology* (in press).

Thomlinson, R. H., Dische, S., Gray, A. J., and Errington, L. E., 1976. Clinical testing of the radiosensitizer Ro–07–0582. 3. Response of tumours. *Clinical Radiology* (in press).

THE EFFECT OF IRRADIATION ON NORMAL HUMAN RECTUM

By D. J. D. Perrins

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When hyperbaric oxygen was first introduced as a radiosensitizer it was suggested that the dose of irradiation might have to be reduced in order to avoid unacceptable damage to normal tissue.

In an attempt to answer this question serial biopsies of normal human rectal mucosa were taken before, during and after a course of radiotherapy in patients with advanced carcinoma of the bladder and cervix uteri. Analysis of the constituent cell types in the crypts of the mucosa revealed that the total number of cells was unaffected whether the irradiation was given in air or hyperbaric oxygen. Although there was a qualitative difference it was not of sufficient magnitude to require adjustment of dose when treating in hyperbaric oxygen.

When a replicating pericryptal fibroblast system was described for the colon, the material was re-examined in the hope that the response of a mesenchymal tissue to irradiation could be measured. The results indicate that during a course of irradiation the fibroblast and the adjacent epithelial cell counts fall. Unlike the epithelial cells however, only some immediate recovery occurs in the fibroblast population; moreover there is a gradually diminishing trend during the first year while the epithelial cell numbers are maintained. It is postulated that this lack of recovery of a connective tissue after irradiation may be an important component of late radiation damage.

REFERENCES

Wiernik, G., and Perrins, D., 1972. The radiosensitivity of normal human rectal mucosa to irradiation in hyperbaric oxygen. *British Journal of Radiology*, *45*, 737–744.

Wiernik, G., and Perrins, D., 1975. The radiosensitivity of a mesenchymal tissue. The pericryptal fibroblast sheath in the human rectal mucosa. *British Journal of Radiology*, *48*, 382–389.

THE EFFECTS OF RADIATION ON THE SKIN BLOOD PULSE

By G. D. Zanelli

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Measurement of the skin blood volume pulse (BVP) is a well-known method for investigating the reaction of the vascular bed to applied internal or external stresses.

We have measured the skin BVP in three patients during and after fractionated radiation treatment for malignant disease. The purpose was to assess the value of the method for quantitating the reaction of human skin to radiation and as a tool for investigating some aspects of radiation damage to the microvasculature of the skin.

The BVP of irradiated skin becomes significantly greater than that of normal skin after a dose of about 1,000 rad has been accumulated and before the appearance of a clearly detectable erythema. It then follows a typical increasing wave pattern. In one patient the BVP in the irradiated skin was as much as nine times greater than that of normal skin. The maximum BVP does not coincide with maximum erythema but follows it some days later. Eight months after irradiation, when the skin has recovered its normal appearance, the BVP is still elevated. Mild cooling, which is sufficient to eliminate pulsations for up to two minutes in normal skin, does not affect the BVP of irradiated skin. It is suggested that radiation alters the elastic properties of either the blood vessels' walls or those of the surrounding tissues, or both.

Skin BVP measurement can be carried out without any discomfort to the patient, even in the presence of a brisk erythema reaction and does not take up much time. It may be valuable in quantitating the skin reaction to radiation and, particularly in conjunction with histology, may yield new information on the nature of radiation damage to the vascular bed.

SOME MEASUREMENTS WITH SKIN AND LYMPHOCYTES

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Full skin thickness biopsy of both an irradiated and a complementary control area of skin permits examination of the histopathological response to radiation of dermal structures. Biopsies have been taken from patients (with informed consent) three or more months after radiotherapeutic régimes totalling three levels of dosage. These can be expressed in CRE units of 4,900 (grid squares receiving 10,000 rad in 10 fractions in 12 days), 1,500 (partial tolerance) and 950 (sub-tolerance). Quantitative histology is possible if counts are made of the number of normal dermal appendages (*e.g.* sweat glands) per section, in serial sections. A dose response was found over the standard therapeutic range but the high-dose samples from grid squares showed changes beyond the limit of resolution. This histometric method can be employed to determine RBE values for DT neutrons, for example.

When patients need palliative radiotherapy to two or more cutaneous deposits of malignant disease then comparable lesions are given different fractionation, predicted to give the same cumulative radiation effect (CRE). A series of patients have provided comparisons of the smaller numbers of fractions (1, 2, 3 and 5 in one week) for which information on time-dose relationships is less frequently available. Most comparisons have satisfied a "null hypothesis" with respect to the biological equivalence of normal and tumour tissue response at the level of partial tolerance.

Peripheral blood from normal human donors has been used to provide samples of lymphocytes (after a ficoll-hypaque gradient procedure which separates more than 90 per cent lymphocytes). Exponential dose-response curves have been obtained with aliquots irradiated before stimulation with phytohaemagglutinin (PHA) and labelled with ^{14}C-thymidine after three or six days' culture. This permits measurement of the transformation index by scintillation counting. The slope of the dose-response curve was different when the concentration of PHA was reduced: The D_0 was 1,000 rad with 5 μg/ml. and 400 rad with 0·5 μg/ml.

(*A number of Glasgow colleagues collaborated in these three studies.*)

A PATIENT WITH ATAXIA-TELANGIECTASIA SHOWING ABNORMAL RADIOSENSITIVITY TO NORMAL DOSES OF IRRADIATION

By Jillian R. Mann

Children's Hospital, Birmingham

Ataxia-telangiectasia is a syndrome of autosomal recessive inheritance characterized by cerebellar ataxia, oculocutaneous telangiectasia, chromosomal instability, immunological deficiencies and an increased incidence of reticulo-endothelial malignancy.

A seven-year-old boy with this disorder developed a malignant lymphoma of the right lung. Since the tumour extended up the bronchus to the plane of resection, radiotherapy was given to the mediastinum in an attempt to eradicate the residual tumour. After 2,000 rad dysphagia was noted and skin erythema occurred in the radiation field, necessitating cessation of the treatment after 3,000 rad had been given. Despite systemic prednisolone therapy, the dysphagia increased, the skin sloughed from the irradiated areas of the chest and the child died nine weeks after the start of radiotherapy (Cunliffe *et al.*, 1975).

Two previous examples of death from radiosensitivity have been reported in patients with ataxia-telangiectasia (Gotoff *et al.*, 1967; Morgan *et al.*, 1968). The possible significance of the radiosensitivity is discussed, and attention is drawn to the hypothetical risk of similar radiosensitivity in two other disorders characterized by chromosomal instability and predisposition to malignancy—Bloom's and Fanconi's syndromes.

REFERENCES

CUNLIFFE, P. N., MANN, J. R., CAMERON, A. H., ROBERTS, K. D., and WARD, H. W. C., 1975. Radiosensitivity in ataxia-telangiectasia. *British Journal of Radiology, 48*, 374–376.

GOTOFF, S. P., AMIRMOKRI, E., and LIEBNER, E. J., 1967. Ataxia telangiectasia—neoplasia, untoward response to X-irradiation and tuberous sclerosis. *American Journal of Diseases of Children, 114*, 617–625.

MORGAN, J. L., HOLCOMB, T. M., and MORRISSEY, R. W., 1968. Radiation reaction in ataxia telangiectasia. *American Journal of Diseases of Children, 116*, 557–558.

ATAXIA TELANGIECTASIA, RADIOSENSITIVITY AT THE CELLULAR AND MOLECULAR LEVEL

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By P. H. M. Lohman

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Fibroblast cell strains from normal human donors and four ataxia telangiectasia (AT) patients have been exposed to γ irradiation. The radiosensitivity of our sample of eight cell lines from normal donors varied by a factor of approximately two, with a mean D_0 value of about 140 rad. The AT cell lines were at least three times as sensitive with a mean D_0 of about 40 rad (Taylor *et al.*, 1975). We were not able to demonstrate any cross-sensitivity of two AT cell strains to ultraviolet light, methyl methanesulphonate or mitomycin C. Thus chemotherapy may be a potential alternative to radiotherapy with these patients although radiotherapy may be possible with scaled-down doses.

At the molecular level AT cells are seen to be normal in their capacity to repair γ-induced single and double strand breaks in DNA but are deficient in the excision repair of a specific type of base damage. Thus it is possible to correlate defective-DNA repair, radiosensitivity in culture and *in vivo* and predisposition to malignant tumours. AT cells appear to be an ionizing-radiation equivalent of xeroderma pigmentosum cells with which considerable success has been achieved in elucidating the repair processes active on UV photoproducts in the DNA of human cells.

REFERENCE

TAYLOR, A. M. R., HARNDEN, D. G., ARLETT, C. F., HARCOURT, S. A., LEHMANN, A. R., STEVENS, S., and BRIDGES, B. A., 1975. Ataxia telangiectasia: a human mutation with abnormal radiation sensitivity. *Nature*, *258*, 427–429.

THE RADIOSENSITIVITY AT THE CHROMOSOMAL LEVEL OF LYMPHOCYTES FROM PATIENTS WITH ATAXIA TELANGIECTASIA

By A. M. R. Taylor, J. A. Metcalfe, J. M. Oxford and D. G. Harnden

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The radiosensitivity of patients with ataxia telangiectasia (AT) has been indicated from *in vivo* studies (Cunliffe *et al.*, 1975) and recently from *in vitro* studies on skin fibroblasts (Taylor *et al.*, 1975). We have also shown, that this radiosensitivity is observed at the chromosomal level in blood lymphocytes, X-irradiated at different stages of the cell cycle and over the same dose range as that used in survival experiments.

Following X-irradiation (200–400 rad) of G_0 lymphocytes from AT patients, an increased number of both chromosome type aberrations and chromatid type aberrations were observed. Chromatid type aberrations of any kind are rarely seen in normal lymphocytes irradiated at G_0, but in the AT lymphocytes many chromatid interchanges including triradials were seen. Irradiation during G_2 induced a very high level of chromatid gaps and breaks in AT lymphocytes compared with controls. This agrees with a previous report (Rary *et al.*, 1974).

Our results are consistent with the hypothesis that there is a defect in the repair of X-ray damage bases in AT cells, the consequences of which can be observed as visible chromosome aberrations, unrepaired single strand damage giving rise to chromatid type aberrations after G_0 irradiation and unrepaired double strand breaks giving both chromosome type aberrations after G_0 and chromatid type aberrations following G_2 irradiation.

Although there are difficulties in extrapolating from events at the molecular level to observations made on chromosomes, the possible role of failure to repair damage in the production of chromosome aberrations has also been shown in cells from patients with xeroderma pigmentosum (Sasaki, 1973).

REFERENCES

CUNLIFFE, P. A., MANN, J. R., CAMERON, A. H., ROBERTS, K. D., and WARD, A. W. C., 1975. Radiosensitivity in ataxia-telangiectasia. *British Journal of Radiology*, *48*, 374–376.

RARY, J. M., BENDER, M. A., and KELLY, T. E., 1974. Cytogenetic studies of ataxia-telangiectasia (abstract), *American Journal of Human Genetics*, *26*, 70A.

SASAKI, M. S., 1973. DNA repair and susceptibility to chromosome breakage in xeroderma pigmentosum cells. *Mutation Research*, *20*, 291–293.

TAYLOR, A. M. R., HARNDEN, D. G., ARLETT, C. F., HARCOURT, S. A., LEHMANN, A. R., STEVENS, S., and BRIDGES, B. A., 1975. Ataxia telangiectasoa: a human mutation with abnormal radiation sensitivity. *Nature*, *258*, 427–429.

Book reviews

Principles of Diagnostic X-ray Apparatus. Edited by D. R. Hill, pp. 383, 1975 (The Macmillan Press Ltd.), £4·95.

This is a very useful book which has been written in such a way as to be valuable for students of diagnostic radiography, for X-ray service engineers, and to anyone concerned with teaching apparatus construction. The emphasis throughout the book is on practical matters. Twelve of the 21 chapters deal with various aspects of the design and use of equipment. These are preceded by a section dealing with the production and measurement of X rays and their interaction with matter; a chapter on radiation physics which would be valuable for radiographers studying for a diploma is included.

The design of test equipment and its application to fault diagnosis is dealt with. The final chapter deals very briefly with items of electromedical equipment such as might be used for clinical monitoring, and that might be used in an X-ray department. This chapter should be regarded as introductory to more extensive publications.

To sum up, the book contains a lot of useful information at a very practical level, and is ideal for teachers in this field. The production of the book would be improved by better reproduction of some of the photographic illustrations.

N. W. RAMSEY.

Flash Radiography. By Frances Jamet and Gustav Thomer, pp. 192, 1976 (The Netherlands, Elsevier Scientific Publishing Company), D.fl.85.

This book describes in detail the theory and design of flash radiography tubes. Flash radiography tubes produce X rays with a dose-rate of 10^5 C $Kg^{-1}s^{-1}$ (10^8 to 10^9 Rs^{-1} approximately) at 1 m, during a pulse lasting a few nanoseconds (10^{-9}s); the dose delivered per flash may vary by 5 to 10 per cent. The high current is obtained by cold emission and vacuum discharge.

Flash radiography has applications in industry for research into short-lived phenomena, but some studies also have been made of impact effects on experimental animals.

It has been suggested that flash techniques might be of value for the radiography of children who cannot be adequately immobilized. An X-ray machine for medical purposes has been made which operates at 350 kV and generates X-ray pulses approximately 20 nanoseconds long with a repetition rate of 1,000 pulses per second, the total number during exposure being controlled by an ionisation chamber. The authors do not refer to any results of medical examinations using such a system.

N. W. RAMSEY.

1976, *British Journal of Radiology*, *49*, 562

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents.)

THE EDITOR—SIR,

A STANDARD SYSTEM OF CO-ORDINATES FOR RADIOTHERAPY APPARATUS

May I use your correspondence column to draw your readers' attention to the proposed code published in *Physics in Medicine and Biology* (1974, *19*, 213–219) for "A standard system of co-ordinates for radiotherapy apparatus".

In brief, the code sets out recommendations for a unique system of scale co-ordinates for the 11 most common movements found on radiotherapy beam units. It was compiled from a survey of 50 installations in 14 departments from 9 manufacturers in an effort to eliminate the confusion that exists in departments when equipment from different manufacturers is installed.

Such uniformity is particularly important when patients, planned on a simulator, are transferred to a treatment unit—scale conversions are time consuming and error prone. Consistency of scale readings is also important when computers are used to assist in treatment planning, to check the treatment set-up or to control the treatment unit movements.

The appendix to the code summarizes the information collated from the survey and the consistency between the (then) existing systems and the recommendations.

Many delegates at the Edinburgh Congress enquired after the publication of this code, demonstrating the keen interest the survey aroused, but at the same time demonstrating that the publication has passed almost unnoticed. I hope this letter will help to publicize the code and speed the implementation of a standard system.

Yours, etc,
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THE EDITOR—SIR,

ELECTRON CONTAMINATION OF TELECOBALT BEAMS

Baum and Phillips (1974), using an experimental set-up, showed that electron contamination could make the surface dose as much as 50 per cent greater than the dose at a point 0·3 cm deep in tissue, even with a collimator-skin distance as large as 20 cm. They emphasized the importance of such contamination in radiotherapy, and showed that the overdosage could be removed by a Perspex (or better still, a copper) filter at the end of the collimator.

The measurements of Baum and Phillips were made under conditions not directly comparable to those in most teletherapy machines. The urgent need for data more directly related to the clinical situation, and the apparently widely held misconception that the electrons come mainly from the parts of the collimator system closest to the patient, prompts us to present some relevant measurements from two different telecobalt machines. A full account will be presented in a later paper on the general problem of electron contamination in high energy photon beams.

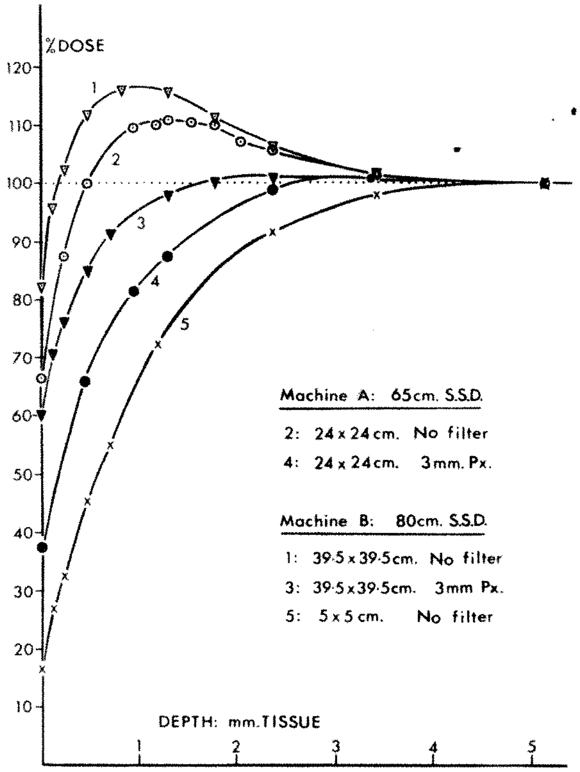

FIG. 1.

Build up measurements for two different cobalt machines.

Machine A (65 cm SSD, collimator–skin distance 30 cm, maximum field 24 × 24 cm) has been used in many countries for the past 18 years, and was supplied already fitted with a Perspex filter across the end of the primary collimating cone, about 12 cm from the source. The rest of the data in Fig. 1 were obtained during the normal commissioning of Machine B (80 cm SSD, collimator–skin distance 35 cm, maximum field 39·5 × 39·5 cm) which was not fitted with an electron filter.* All field sizes mentioned here are defined by the 80 per cent isodose lines at 0·5 cm depth in a water phantom.

The results obtained so far show:

(1) a peak dose of about 116 per cent about 0·1 cm below the surface in a 39·5 × 39·5 cm field (Machine B);
(2) experiments with magnetic fields have shown that this peak is due to electrons with penetration corresponding to an average energy of about 600 keV;
(3) the electron flux is very dependent on field size, becoming unacceptable above about 25 × 25 cm (at 80 cm SSD, Machine B);
(4) the size of the peak increases as the SSD decreases, up to 132 per cent at 65 cm for Machine B;
(5) in nearly all situations, the surface dose remains less than the dose measured at 0·5 cm depth;
(6) a suitable filter (*e.g.* about 0·3 cm Perspex) removes the problem of overdosage at all field sizes and for all practical treating distances;
(7) lining the collimator surfaces with medium Z material (*e.g.* brass) reduces the peak dose by only about 7 per cent;

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*Since these measurements were made the manufacturers of Machine B have provided attachable Perspex filters for all machines of this design. The resulting build-up curves for the larger field sizes are then similar to Curve 3 of Fig. 1.

1976, *British Journal of Radiology*, *49*, 563–564

(8) doses greater than the 100 per cent measured 0·5 cm deep on the beam axis occur over the central 24 × 24 cm area of the 39·5 × 39·5 cm maximum field (Machine B);

(9) the electron flux extends a long way beyond the geometrical edge of the photon beam, giving a high "hidden" surface dose in regions where negligible dose is usually shown on isodose charts drawn for depths greater than 0·5 cm;

(10) measurements with filters at different distances from the source have shown that the electron flux from the patient end of the collimator system is negligible compared with the flux from the surface of the primary collimator cone close to the source.

Several important points arise from these measurements, and from the published literature on telecobalt machines.

1. It is essential that measurements are made throughout the build-up region when commissioning new teletherapy machines, as the overdosage peak may lie below the surface. Measurement of the surface dose alone is not a sufficient test for electron contamination.

2. Skin sparing can be lost completely even under conditions that conform to current international recommendations. For example, I.C.R.U. Report 10d on *Clinical Dosimetry* (1963) gives the misleading advice that overdosage in the build-up region will not occur if the collimators are more than 15 cm from the skin. This is repeated in I.C.R.U. Report 10b on *Physical Aspects of Irradiation* (1964). Similarly, the chapter by Johns in *Radiation Dosimetry* by Attix *et al.* (1969) (Vol. III, p.30) states that such peaks occur only when scattering objects are close to the skin. It does not seem to be widely appreciated that an electron filter is necessary in the beam even when all collimators are further than 15 cm from the skin, although Haybittle (1955) does mention that a filter cuts out these electrons. There seems to be a widespread belief among both users and manufacturers of cobalt machines that the main purpose of a filter at the end of the primary cone is to prevent objects falling in rather than to stop electrons getting out.

3. The necessity of fitting an electron filter considerably influences the design of a cobalt collimator system, and the later addition of a filter to a machine not designed to take one can raise problems.

4. High surface doses outside the geometrical edge of the beam can lead to high combined doses and hence unexpected reactions when two adjacent fields are used together, or when a second field is treated some time later.

5. Because the overdosage peak increases rapidly with decreasing SSD, electron contamination should be checked over a range of SSD if treatment techniques are used which place the tumour at the centre of rotation.

Theory predicts that the primary cone provides the majority of electrons, since the γ flux causing the emission decreases as the square of the distance from the source, whereas the surface area of the collimator increases only linearly with distance. Therefore the electron flux produced decreases approximately linearly with distance from the source, and this is only slightly offset by the decreasing distance to the skin in machines with a large SSD. The electrons generated by the filter are approximately independent of source-filter distance, since the increase in filter area with distance is compensated by the decrease in γ flux at the filter. The area of the collimator surfaces between filter and source is approximately four times the surface area of the filter, and therefore the filter removes far more electrons than it generates.

In conclusion, some means for removing electrons is essential in the design of telecobalt machines, especially when used to treat large fields.

Yours etc.,
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REFERENCES

BAUM, J. W., and PHILLIPS, L. F., 1974. Minimizing surface dose with medium Z electron shields. *Physics in Medicine and Biology*, 19, 223–225.

HAYBITTLE, J. L., 1955. Physical requirements of beam defining systems for medium distance teletherapy units. *Acta Radiologica*, *44*, 505–520.

THE EDITOR—SIR,

GAMMA-RAY SCATTER IN A TELECOBALT BEAM

Over the past four decades many measurements have been reported on contamination in γ-ray beams. Originally these related to short distance radium units and later to teletherapy cobalt units. The effects of electron contamination are well known. The effects of scattered γ-ray photons have been presented in the past from the point of view of photon spectra in clinical beams, and the contribution made by the lower energy scattered photons to the measured dose-rate in the clinical beam.

This letter presents a preliminary report of measurements made at the Christian Medical College and Hospital, Vellore, on the clinical beam from a Theratron-60 teletherapy cobalt unit.

A medium atomic number brass filter has been used in the usual way to eliminate electron contamination. Spectral measurements of the resultant clinical γ-ray beam showed a high proportion of scattered photons present in the beam, which contributed approximately one-third of the dose-rate. Maximum dose build-up was found to occur at a depth

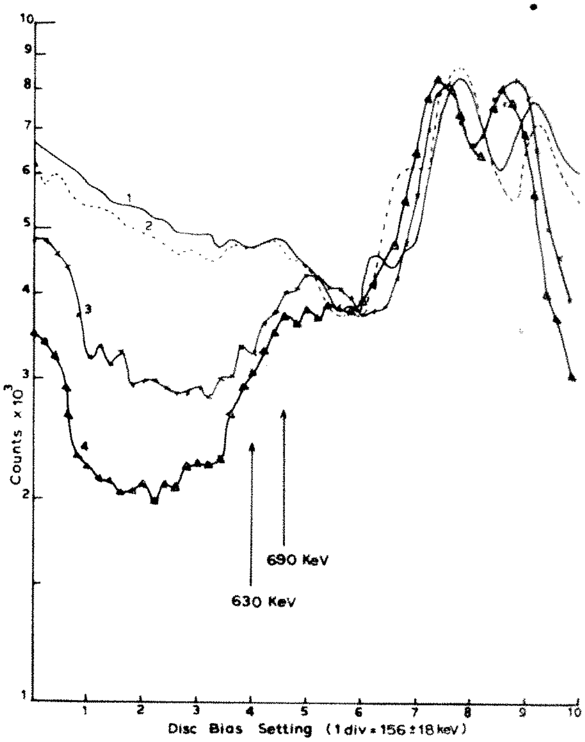

FIG. 1.

γ-ray spectra of the beam from the Theratron-60 telecobalt unit.

1. Spectrum of the unfiltered γ-ray beam. 2. Spectrum with 1·5 mm brass electron filter. 3. Spectrum with 3 mm lead filter. 4. Spectrum with 4·5 mm lead filter.

of only 3 mm, this depth being affected by the energy of the incident scattered photons.

The effect of high atomic number filtration on the beam spectrum has been investigated and it has been found that the proportion of scattered photons can be significantly reduced by a lead filter. The effect of this filtration on photon energy in the beam is shown in Fig. 1. This shows the spectra, measured using a sodium iodide crystal detector, of the unfiltered beam, of the beam after passing through a brass filter to remove electrons, and after passing through a 3 mm and through a 4·5 mm lead filter.

It is recommended that lead glass of 3 mm lead equivalent be provided as an external filter. This would give a beam with maximum build up at 5·5 mm below the skin, and would allow the normal use of the optical beam defining system.

Yours etc.,
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THE EDITOR—SIR,

APPLICATION OF THE WEIBULL DISTRIBUTION

Having derived a Weibull equation from a very simple biological model of age-dependent disease, and having applied it extensively for more than a decade, I was disturbed to read in your November issue (Campos, 1975) that the equation "has no particular theoretical basis". The model can be described briefly: A disease is restricted to a sub-population that comprises a fraction, S, of the general population; it is initiated by r random somatic gene mutations (where r is a positive integer) that are accumulated in a single stem cell. It follows from certain assumptions (see below) that the age-specific initiation rate ($\mathrm{d}P/\mathrm{d}t$) at age t years will be described by the Weibull equation (Burch, 1965, 1966).

$$\mathrm{d}P/\mathrm{d}t = rkSt^{r-1}\exp(-kt^r) \quad . \quad . \quad . \quad (1)$$

where $k = Lm^r$. Here L ($\geqslant 1$) is the number of stem cells at somatic mutational risk per person at risk; and m is the average rate of mutation for each of the r genes at risk per cell at risk per year. The equation requires that:

(1) $mt \ll 1$ for all t of interest;
(2) back mutation has a negligible impact;
(3) S remains effectively constant with time; and
(4) the average overall age-specific mortality in the predisposed sub-population resembles that in the general population.

Equation (1) is a particular version of the following more general equation (Burch, 1966, 1968) which appears to be relevant to the great majority of diseases that exhibit a reproducible age-pattern:

$$\mathrm{d}P/\mathrm{d}t = \{nrkSt^{r-1}\exp(-kt^r)\}\{1-\exp(-kt^r)\}^{n-1} \quad . \quad (2)$$

Parameter n represents the number of distinctive (independent) stem cells, each of which has to acquire r random initiating somatic mutations. With $r = 1$, we have a Yule distribution:

$$\mathrm{d}P/\mathrm{d}t = \{nkSt\exp(-kt)\}\{1-\exp(-kt)\}^{n-1} \quad . \quad . \quad (3)$$

Equations of the same general form as the integrated versions of (1) and (3) also describe (Burch, 1970a, b) the relation observed in many radiobiological systems between effective target cross-section (A_L) and LET (L) in track-segment experiments.

The Weibull equation,

$$A_L \doteq A\{1-\exp(-kL^r); \quad . \quad . \quad . \quad (4)$$

will apply when:

(1) the system (for example, chromosome, cell, etc.) consists of numerous, complex targets, each consisting of r distinctive elements;
(2) the probability that any one specific element will receive an effective radiation "hit" is small at all L of interest; and
(3) biological change depends on each of the r elements, of at least one complex target, receiving an effective radiation "hit".

Equations (1) to (3) of the model of age-dependent disease are the mathematical consequences of the stochastic nature of gene mutation, the specificity of a gene and the specificity of distinctive cells. Equation (4) is the mathematical consequence of the stochastic nature of energy transfers from ionizing particles and the structural specificity of complex biological molecules such as double-stranded DNA. A restriction that is common to both models should be emphasized: the parameter r in the Weibull equations and n in the Yule equations must be positive integers.

Yours, etc.,
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REFERENCES

BURCH, P. R. J., 1965. Natural and radiation carcinogenesis in man. I. Theory of initiation phase. *Proceedings of the Royal Society*, *B 162*, 223–239.

1966. Spontaneous auto-immunity: equations for age-specific prevalence and initiation-rates. *Journal of Theoretical Biology*, *12*, 397–409.

1968. *An Inquiry Concerning Growth, Disease and Ageing*, (Oliver and Boyd, Edinburgh).

1970a. Track structure in relation to target structure. In: *Proceedings of the Second Symposium on Microdosimetry*, 685–708. Editor H. G. Ebert. Commission of the European Communities, Brussels.

1970b. Stochastic equations relating RBE to LET. In *Charged Particle Tracks in Solids and Liquids*, 127–139. Eds. G. E. Adams, D. K. Bewley and J. W. Boag. The Institute of Physics and The Physical Society Conference Series No. 8, London.

CAMPOS, J. L., 1975. Application of the Weibull distribution to some instances of cell survival; of neoplastic survival, and of ageing. *British Journal of Radiology*, *48*, 913–917.

THE EDITOR—SIR,

ACCEPTABLE RADIATION TREATMENT SCHEDULES TO THE KIDNEY

If radiation response in the pig is sufficiently similar to that in the human for the experimental results of Hopewell and Berry (1974) to be transferable to the clinical situation, the following treatment schedule would appear not to exceed tolerance for the kidney:

(1) a single X-ray dose of 1,000 rad (equivalent to approximately 1,100 rad with ^{60}Co);
(2) Six X-ray doses of 243 rad over 18 days (equivalent to 6 × 270 rad with ^{60}Co);
(3) 30 X-ray doses of 121 rad over 30 days (equivalent to 30 × 134 rad with ^{60}Co).

An NSD of 1,800 rads, which is assumed to apply for connective tissue, corresponds (Ellis, 1968) to some 22 treatments of 270 rad given twice a week or 57 treatments of 134 rad given five times per week. On the basis of calculation of "partial tolerance", the above schedules are therefore equivalent to 1,100 rets, $6/22 \times 1{,}800 = 416$ rets, and $30/57 \times 1{,}800 = 954$ rets respectively.

However, it may be that, with small doses, all late clinical damage is not obvious in the six months of this study, and, on the basis of the clinical data of Kunkler *et al.* (1952), I have suggested (Ellis, 1968) an acceptable tolerance for the kidney of only $0 \cdot 2 \times 1{,}800 = 360$ rets. Any radiotherapist exceeding this figure may put his patient in jeopardy and the following corresponding equivalent schedules may then be calculated similarly:

(1) a single dose of 360 rad;
(2) six treatments of 220 rad twice weekly over 18 days;
(3) 30 treatments of 70–75 rad five times weekly over 39 days.

When further information is available about radiation damage in the kidney, say after one year, for patients who have received larger doses accidently or of necessity, there may be justification for exceeding these figures. However, the mechanisms of both early and late damage to the kidney, which are responsible for its great sensitivity as demonstrated in clinical work, are not yet understood. Until they are, or until more clinical facts are available, the doses suggested above should not be significantly exceeded.

Yours, etc.,
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REFERENCES

ELLIS, F., 1968. The relationship of biological effect to dose-time-fractionation factors in radiotherapy. *Current Topics in Radiation Research*, *4*, 357–397.

HOPEWELL, J. W. and BERRY, R. J., 1974. The predictive value of the NSD system for renal tolerance to fractionated X-irradiation in the pig. *British Journal of Radiology*, *47*, 679–686.

KUNKLER, P. B., FARR, R. F. and LUXTON, R. W., 1952. The limit of renal tolerance to X-rays. *British Journal of Radiology*, *25*, 190–201.

Editor's note

This letter was originally received in January 1975, but due to prolonged correspondence between the author and several other doctors who were involved in similar work, publication has been delayed until now.

THE EDITOR—SIR,

NSD AND EXPERIMENTAL WORK WITH PIGS

Berry and his colleagues have recently described their interesting and excellent experimental work in the pig (Berry *et al.*, Patterson 1974a; Berry *et al.*, 1974b). However, I would point out that they have not used the NSD concept correctly when calculating equivalent biological effects. Two factors must be borne in mind:

(1) The formula applies to ^{60}Co therapy and the corresponding doses for 250 kV X-radiation must be obtained by multiplying by 0·9.
(2) The partial tolerance principle must be used in calculating ret doses.

In the table the ret doses corresponding to their treatment schedules have been recalculated using the NSD slide-rule (Winston *et al.*, 1969). The dose per fraction, corrected to relate to ^{60}Co radiation, is set against the frequency of treatment (2 or 5 fractions per week) to give the number of fractions, *N*, for an NSD of 1,800 rets. The ret dose corresponding to the treatment is then calculated from the ratio 1,800/N multiplied by 6 or 30, the number of fractions actually used. It is clear that all their treatments provided ret doses in excess of those intended, and the last two columns show the X-ray doses which should have been given in each case. However, the ret doses given in the two régimes of fractionation are still very similar to one another.

Yours, etc.,
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REFERENCES

BERRY, R. J., WIERNIK, G., and PATTERSON, T. J. S., 1974a. Skin tolerance to fractionated X-irradiation in the pig—how good a predictor is the NSD formula. *British Journal of Radiology*, *47*, 185–190.

BERRY, R. J., WIERNIK, G., PATTERSON, T. J. S., and HOPEWELL, J. W., 1974b. Subcutaneous fibrosis after irradiation of pig skin upon the application of the NSD formula. *British Journal of Radiology*, *47*, 277–281.

WINSTON, B. M., ELLIS, F., and HALL, E. J., 1969. The Oxford NSD calculator for clinical use. *Clinical Radiology*, *20*, 8–11.

Editor's note

This letter was originally received in January 1975, but due to prolonged correspondence between the author and several other doctors who were involved in similar work, publication has been delayed until now.

TABLE I

6 fractions in 18 days 250 kV X-ray dose (rad)	Dose/fr. (rad)	Equiv. ^{60}Co (rad)	Number of fractions for 1,800 rets	Rets given	Rets intended	250 kV X-ray dose for rets intended (rad)
3,790	632	702	5·1	2,118	1,800	6 × 572 = 3,432
4,350	725	806	4·1	2,634	2,070	6 × 658 = 3,948
4,920	820	911	3·35	3,224	2,340	6 × 743 = 4,358
5,490	915	1,017	2·85	3,803	2,610	6 × 830 = 4,980
30 fractions in 39 days						
5,230	174	193	32·8	1,646	1,530	30 × 156 = 4,680
6,150	205	228	25·5	2,118	1,800	30 × 183 = 5,490
7,080	236	262	20·4	2,647	2,070	30 × 210 = 6,300
8,000	267	297	16·8	3,214	2,340	30 × 238 = 7,140
8,920	297	330	14·4	3,750	2,610	30 × 264 = 7,920

1976, *British Journal of Radiology*, *49*, 566–567

Correspondence

THE EDITOR—SIR,

HUMAN LYMPHOCYTE TRANSFORMATION BY PHYTOHAEMAGGLUTININ AFTER "IN VITRO" AND "IN VIVO" IRRADIATION

Your correspondents, Song and Levitt (1975), queried our results on lymphocyte transformation by PHA after *in vitro* irradiation. They suggested that our results conflicted with other published data and they referred specifically to the work of Conrad (1969) which, in their opinion, supported their own findings that PHA transformation of lymphocytes from rats was not significantly depressed by 1,000 rad of X-irradiation. Conrad (1969) constructed a response curve for maximum effect, *i.e.* after three days incubation, a time used in our own studies, and showed that for an X-ray dose of 750 rad inhibition of lymphocyte transformation occurred and the response was 38 per cent of that observed at zero dose, while at higher doses a levelling off in response was seen (Fig. 1). Our data after three days' incubation showed that the response was 25 per cent of that at zero dose for 750 rad of γ rays with a similar levelling off at higher doses. Ilbery *et al.*, (1971) carried out similar experiments with human lymphocytes after *in vitro* γ irradiation and showed that the response was 35 per cent of that at zero dose for 750 rad with a similar tendency to level off at high doses (Fig. 1).

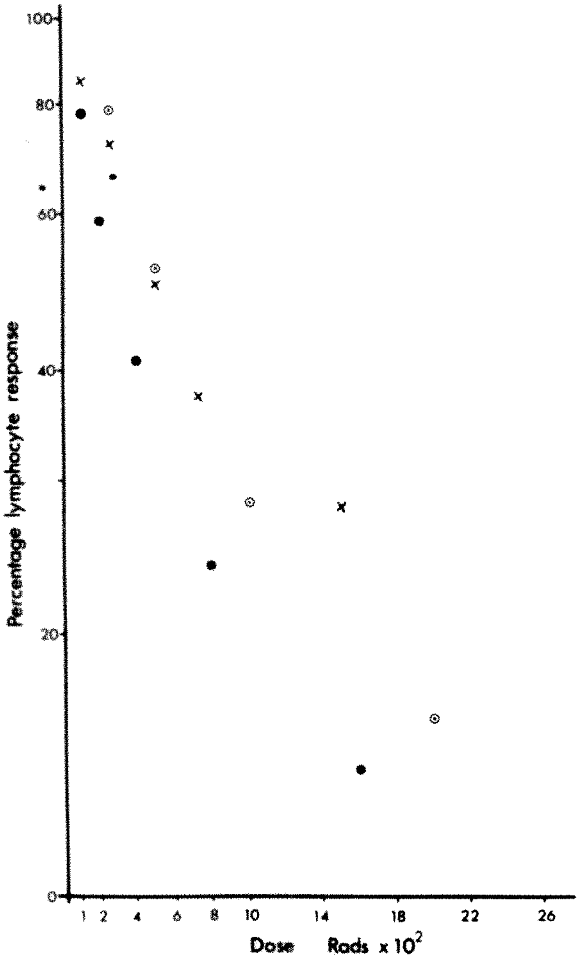

FIG. 1

Response of human lymphocytes to PHA after *in vitro* irradiation; ●, Braeman and Moore 1974; X, Conrad 1969; ○, Ilbery *et al.*, 1971.

Work by Nias (1975) not yet published showed that 1,000 rad reduced PHA transformation to approximately 35 per cent of that at zero dose. These results with human lymphocytes are really very similar considering the different techniques used to measure lymphocyte response to PHA. In our experiments (Braeman and Moore, 1974) a microscopic morphological technique was used; Conrad (1969) used electronic counting and sizing of nuclei and Ilbery *et al.* (1971) and Nias (1975) used incorporation of tritiated thymidine. The results of all these investigations are plotted in Fig. 1. Since it is the radiosensitivity of lymphocyte response to PHA transformation that is being measured, the data from all three investigations were plotted using the conventional semi-logarithmic plot used in radiation studies. From this graph a dose of 400–600 rad reduced the response to 40 per cent of that observed when no radiation was given, and in each case a levelling off in effect is seen at higher doses.

Song and Levitt (1975) quoted the work of Neff and Cassen (1968) who demonstrated that damaged lymphocytes were rapidly removed from circulation following *in vivo* irradiation. This work was carried out with rabbits and caution must always be exercised when extrapolating animal results to humans. However, Neff and Cassen (1968) also measured the effect of *in vitro* irradiation on lymphocyte transformation by PHA and noted for 300 rad of X-irradiation the response was 80 per cent of that observed for zero dose after three days incubation, a loss of response comparable to that reported by these other workers for human lymphocytes. Care must also be taken when comparing data obtained after three days incubation with that seen after six days incubation.

It was possible to obtain blood samples, before and immediately after irradiation, from some patients being treated at Velindre Hospital. The samples taken before irradiation were then irradiated *in vitro* with the same dose as that given to the patient. Obviously the lymphocytes would receive a smaller dose from the *in vivo* treatment and a smaller loss in PHA transformation would be expected. The results are shown in Table I and demonstrate that both *in vivo* and *in vitro* irradiation depress response of lymphocytes to PHA. Patient E is additionally interesting since the tumour was a basal cell carcinoma on the nose which was irradiated with superficial X rays so no significant dose would be given to the lymphocytes; this is clearly seen in the unchanged response of the lymphocytes after *in vivo* irradiation.

TABLE I

LYMPHOCYTE TRANSFORMATION BY PHA AFTER "IN VIVO" AND "IN VITRO" IRRADIATION AS A PERCENTAGE OF THAT SEEN AT ZERO DOSE.

			% PHA transformation	
Patient	Dose (rad)	Tumour site	*in vivo* irradiation	*in vitro* irradiation
A	223	Larynx	91	89
B	500	Parotid	78	65
C	268	Breast	91	67
D	400	Breast	93	55
E	2,000	BCC	100	40

Patients A, B, C, D treated by ^{60}Co γ rays and Patient E with 110 kVp X rays.

1976, *British Journal of Radiology*, *49*, 567–568

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Where samples of blood have been taken before and immediately after irradiation, *i.e.* approximately 15 minutes after completion of treatment, total white cell counts and differential white cell counts were not significantly different.

We feel that in spite of Song and Levitt's (1975) accusation that our results are atypical, it does seem that a closer examination of other people's data shows that we agree with most *in vitro* studies that have been carried out on lymphocyte transformation after irradiation and the suggestions in the original letter are still valid.

Yours, etc,
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JUDITH BRAEMAN.

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REFERENCES

BRAEMAN, J., and MOORE, J. L., 1974. The lymphocyte response to phytohaemagglutinin after *in vitro* irradiation. *British Journal of Radiology*, *47*, 297.

CONRAD, R. A., 1969. Quantitative study of radiation effects of phytohaemagglutinin-stimulated leukocyte cultures. *International Journal of Radiation Biology*, *16*, 157–165.

ILBERY, P. L. T., RICKINSON, A. B., and THRUM, C. E., 1971. Blood lymphocyte replicating ability as a measurement of radiation dosage. *British Journal of Radiology*, *44*, 834–840.

NIAS, A. H. W., 1975. Personal communications.

NEFF, R. D., and CASSEN, B., 1968. Relative radiation sensitivity of circulating small and large lymphocytes. *Journal of Nuclear Medicine*, *9*, 402–405.

SONG, C. W., and LEVITT, S. H., 1975. The lymphocyte response to phytohaemagglutinin after *in vitro* irradiation. *British Journal of Radiology*, *48*, 504.

THE EDITOR—SIR,

HYPOXIC RADIOSENSITIZERS AND CELLULAR RESPIRATION

In a recent communication, Rauth and Kaufman (1975) presented data demonstrating radiosensitization of hypoxic tumour cells with specific drugs and injection techniques. They stressed that radiosensitization *in vivo* is dependent on (1) drug transport to the tumour, (2) diffusion of the drug to the hypoxic cells, and (3) drug effectiveness at high cell density. Inherent in these points, yet worthy of further emphasis, is the requirement that such drugs should have little or no metabolic effect on either the normal or malignant tissues. Changes in cellular metabolism, including respiration, may drastically alter the radiosensitivity of multicellular structures including both tumours (Biaglow *et al.*, 1970) and the *in vitro* spheroid system (Durand and Biaglow, 1974).

Rauth and Kaufman observed that the nitro-imidazoles were the only drugs which resulted in tumour sensitization after intraperitoneal injection. However, relatively good sensitization occurred after localized (intra-tumour) injection of both NDPP and metronidazole (Flagyl). These observations may be partially explained on the basis of the drug concentrations necessary in the tumour for radiosensitization. Another factor which should be considered is the influence of these drugs on cellular oxygen utilization.

We have observed pronounced effects on the oxygen consumption of V–79 cells by Flagyl, NF–167 and NDPP, three of the drugs used by Rauth and Kaufman (Fig. 1). Flagyl inhibited and NF-167 stimulated oxygen utilization at all concentrations. A more complex response was observed with NDPP, as oxygen utilization was stimulated at low drug concentrations and inhibited at higher drug levels. Concentrations of NDPP in excess of 0·5 mM were found to be cytotoxic, and the decreasing respiration at these concentrations (Fig. 1) probably reflects, in part, this toxicity.

Spheroids irradiated in the presence of 0·5 mM NDPP (Fig. 2) showed an initial increase of radio-resistance. This concentration produced a 70 per cent increase in the rate of oxygen utilization (Fig. 1) and apparently increased the hypoxic fraction of the spheroid sufficiently to offset the "direct" sensitizing effect of NDPP. Slight sensitization occurred initially at the *lower* NDPP concentration of 0·125 mM where the hypoxic fraction was not increased as markedly. Sensitization with this low drug concentration reflects both adequate transport of the sensitizer to the hypoxic cells of the spheroids, and virtually "unlimited" drug replacement from the surrounding medium. A similar situation would be extremely difficult to achieve *in vivo* unless the drug were not metabolized and were uniformly distributed. The decline in effect with time, both *in vivo* and *in vitro* (Fig. 2), is probably linked to drug metabolism. This would, of course, develop more slowly in the spheroid system due to the smaller number of cells.

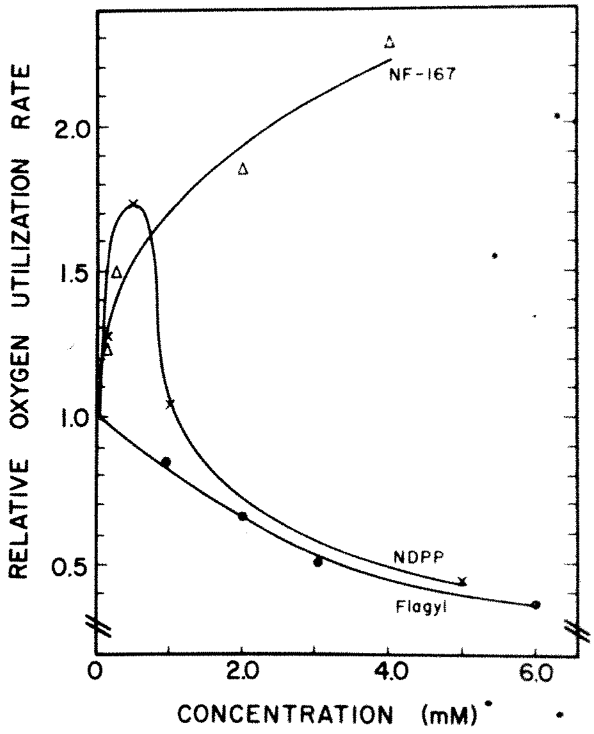

FIG. 1.

Immediate effects of increasing concentrations of freshly prepared NDPP, NF-167 and Flagyl on respiration rate of V79 Chinese hamster cells in suspension. For experimental details, see Biaglow and Durand, 1976.

In the tumour system used by Rauth and Kaufman, as in the *in vitro* spheroid, the net radiosensitivity is in part a function of cellular oxygen utilization and hence the size of the hypoxic cell population. Thus, we would predict that sensitizers which markedly increase oxygen utilization of the well-vascularized areas of a tumour (*e.g.* NF-167, Fig. 1) would always lead to an increase in the hypoxic fraction that could only be counterbalanced by a potent radiosensitizing potential. Conversely, sensitizing concentrations of drugs that inhibit cell respiration (*e.g.* Flagyl, Fig. 1) would always be expected to increase radiosensitivity through both oxygen-like radiosensitization and partial reoxygenation. Both predictions are consistent with Rauth and Kaufman's observations with their *in vivo* system and

1976, *British Journal of Radiology*, *49*, 568–569

Correspondence

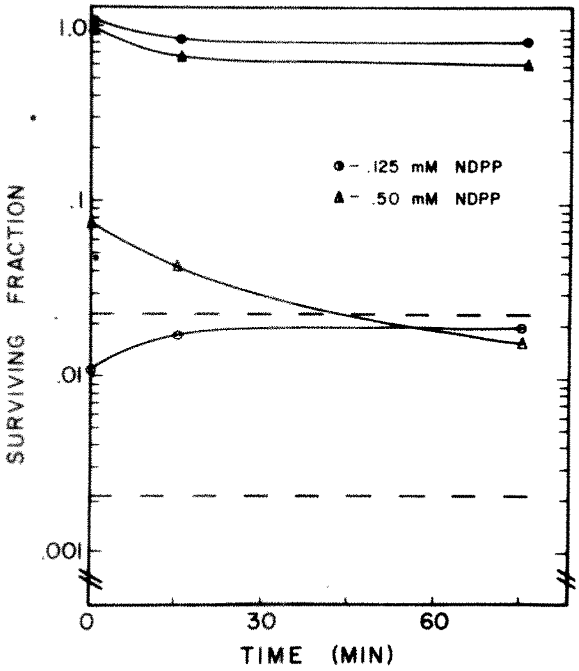

FIG. 2.

Cytotoxicity (closed symbols) and radiosensitizing effect (open symbols, cellular survival after a dose of 1,800 rad) of indicated concentrations of NDPP as a function of time of pre-irradiation incubation with the drug. The upper broken line represents cell survival of untreated spheroids after 1,800 rad; the lower broken line is the survival obtained for fully reoxygenated cells prepared by trypsinizing the spheroids prior to irradiation.

injection techniques. Between these extremes, agents may exhibit both concentration- (NDPP, Figs. 1 and 2) and time-dependent (Fig. 2, and Sutherland and Richardson, 1974) effects. Some agents (*e.g.* Flagyl) may also selectively kill non-cycling cells (Sutherland, 1974). These effects, including inhibition of oxygen utilization, killing of hypoxic cells, and radiosensitizing properties will make it difficult to determine the exact mechanism of sensitization of such agents *in vivo*. However all of these properties would appear to be desirable in choosing a sensitizer for tumours.

Our results and those of Rauth and Kaufman thus indicate that radiosensitizing chemicals may have "secondary" properties which modify their net effectiveness *in vivo*. Specifically, effects on oxygen utilization may modify the radio-response of multicellular systems by modifying the size of the hypoxic fraction. As a consequence, we feel that it is unlikely that any hypoxic-cell radiosensitizer which stimulates oxygen utilization will be particularly effective *in vivo*. In the spheroid system, at least, the effects on oxygen utilization have generally been found to dominate (Biaglow and Durand, 1976). This is not surprising, in view of the fact that molecular oxygen is the most effective radiosensitizer known for hypoxic cells.

ACKNOWLEDGMENTS

Flagyl was a gift of Searle Co. NDPP was supplied by G. E. Adams and the NF-167 was given to us by J. D. Chapman. This investigation was supported in part by Ontario Cancer Foundation Grant No. 227, and by Public Health Research Grant No. CA-13747 from the National Cancer Institute.

Yours, etc.,
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REFERENCES

BIAGLOW, J. E., and DURAND, R. E., 1976. The effects of nitrobenzene derivatives on oxygen utilization and radiation response of an *in vitro* tumor model. *Radiation Research 65*, 529–539.

BIAGLOW, J. E., FERENCZ, N., and FRIEDELL, H. L., 1970. A metabolic control for the enhancement of radiation response. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *108*, 405–411.

DURAND, R. E., and BIAGLOW, J. E., 1974. Modification of the radiation response of an *in vitro* tumour model by control of cellular respiration. *International Journal of Radiation Biology*, *26*, 597–601.

RAUTH, A. M., and KAUFMAN, K., 1975. *In vivo* testing of hypoxic radiosensitizers using the KHT murine tumour assayed by the lung-colony technique. *British Journal of Radiology*, *48*, 209–220.

SUTHERLAND, R. M., 1974. Selective chemotherapy of non-cycling cells in an *in vitro* tumor model. *Cancer Research*, *34*, 3501–3503.

SUTHERLAND, R. M., and RICHARDSON, J., 1974. Radiosensitization of chronically hypoxic cells in multicellular spheroids. *Radiation Research*, *59*, 159.

THE EDITOR—SIR,

WHEN ARE FUME-CUPBOARDS NECESSARY IN HOSPITAL RADIOISOTOPE LABORATORIES?

In a recent letter, Dr. Moore questions the necessity for equipping hospital radioisotope laboratories with fume-cupboards "unless the procedures involved are exceptionally hazardous" (Moore, 1975). A considerable expenditure is being incurred unnecessarily if these fittings are provided where there is no real need, and therefore guidance as to what constitutes "exceptionally hazardous" work would be very valuable. The responsibility of making a decision as to whether a fume-cupboard is necessary or not in any new or modified radioisotope department must rest with the local Radiological Protection Adviser (Code of Practice, 1972) who will judge the various factors involved in the light of his experience. Factors to be considered will include the type of department, the work to be undertaken there, the staff to be involved, and a guess as to the work which may become necessary in the future. The local pharmacist will advise on matters relating to sterility of materials for injection. It is unlikely that the many hospital departments which nowadays use radioisotope methods in their own fields will each need a fume-cupboard, though all those which perform *in vivo* procedures will require a supply of sterile materials. In certain departments the use of an aseptic cabinet may be all that is necessary, *e.g.* during the labelling of blood cells or plasma. This cabinet will be rather similar in appearance to a small fume-cupboard, but there is no requirement for an air-flow and exhaust system so that the cost is relatively trivial.

1976, *British Journal of Radiology*, *49*, 569–570 JUNE 1976

Correspondence

In many X-ray departments where radioisotope scanning is undertaken a considerable quantity of radioactivity, mainly short-lived $^{99}\mathrm{Tc}^{\mathrm{m}}$ and $^{113}\mathrm{In}^{\mathrm{m}}$, will be used. Generators of these isotopes are supplied in a sterile condition and require repeated aseptic elution. The sterility requirements are best satisfied by a closed elution system where the isotope is never exposed to the free air, so that again a fume-cupboard with air-flow and exhaust system may not be required under normal conditions. Tests in this hospital have shown, however, that small quantities of radioactivity may be released through the air-bleed needle which is fitted to the final collecting-vial. The vapour or aerosol emitted can be trapped in a small piece of cotton wool placed around the outlet of the air-bleed needle, otherwise the elution procedure must be done inside the fume-cupboard. It would be preferable to draw the eluent through the generator using a partially evacuated collecting-vial or another syringe.

There are an increasing number of departments which undertake the preparation of sterile radiopharmaceuticals for organ imaging, using a selection of the many recipes that have been published in recent years. It is not always possible to use Millipore filters for sterilization of the final product (*e.g.* in the case of technetium–sulphur colloid) and often the final sterilization is conveniently and satisfactorily carried out using a domestic pressure-cooker (Pearson, 1971). If the slightest amount of radioactivity remains on the outside of a vial, for example, where the rubber cap has been pierced by a hypodermic needle, contamination of the water vapour inside the pressure-cooker will occur and radioactivity will be present in the emitted steam. Such sterilization, therefore, is best performed inside the fume-cupboard.

Storage of therapeutic quantities of $^{131}\mathrm{I}$, because of the volatility and high radiotoxicity of this nuclide, requires a well ventilated area, and the Code of Practice suggests that a lockable fume-cupboard may be the best place for storing this radionuclide. Dispensing and administration of therapeutic doses of radioiodine should also be performed, in my view, in a well ventilated area or fume-cupboard.

Airborne radioactive contamination may also arise when disposable syringes fitted with small-bore hypodermic needles are used to dispense radioisotopes. The use of such needles can easily result in aerosol sprays being produced, particularly when the syringe is almost emptied. When this method is employed, other than into a sealed container, the syringe should be emptied with the tip of the needle below a liquid surface or touching the side of the receiving vessel.

There might be justification therefore for the installation of efficient fume-cupboards (Hughes, 1974) in hospital laboratories that are routinely concerned with the elution of isotope generators, the sterilization of radio-pharmaceuticals involving the use of a pressure cooker, and the storage and handling of therapeutic quantities of $^{131}\mathrm{I}$. I believe it is true that Madame Curie, rather fortuitously, occupied a laboratory that was no more than a draughty wooden shed when she extracted radium from pitchblende ore. Although I do not advocate that hospital radioisotope laboratories are set up in similar accommodation, it would appear that the copious general ventilation of isotope rooms is perhaps better than the too frequent incorporation of unnecessary fume-cupboards.

Yours, etc.,
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REFERENCES

Code of Practice for the Protection of Persons against Ionizing Radiations arising from Medical and Dental Use, 1972. (H.M.S.O., London.)

HUGHES, D., 1974. The design and installation of efficient fume-cupboards. *British Journal of Radiology*, *47*, 888–892.

MOORE, R. D., 1975. Containment of unsealed sources of radionuclides in hospitals. *British Journal of Radiology*, *48*, 410.

PEARSON, J. D., 1971. Procurement and preparation of radioisotopes and labelled compounds. In *Radioisotopes in Medical Diagnosis*. Edited by E. H. Belcher and H. Vetter, pp. 218–235 (Butterworths, London).

THE EDITOR—SIR,

RADIATION EXPOSURE RATES ON SYRINGE SURFACES FROM $^{99}\mathrm{Tc}^{\mathrm{m}}$

A recent article (Henson, 1973) considered possible skin doses and dose-rates from unshielded plastic syringes containing radioactive liquids. In private correspondence, Hušák pointed out that the results given for $^{99}\mathrm{Tc}^{\mathrm{m}}$ differed significantly from his own published data (Hušák, 1971). This letter contains the results of a subsequent comparison of measurements of surface exposure-rates and calculations, and may be of interest to others who have noted the range of values reported in the literature.

Measurements of surface exposure-rate over the mid-point of the syringe active volume were made by two of us (V.H. and J.T.) using LiF-Teflon thermoluminescent dosimeters (TLD). Two discs 0·4 mm thick by 13 mm diameter were taped to syringes, the volumes, inner and outer radii of which were: 2 ml. (4·7 mm, 5·2 mm), 5 ml. (6·0 mm, 6·8 mm), 10 ml. (8·0 mm, 8·8 mm), 20 ml. (9·9 mm, 10·7 mm). The TLDs were calibrated with X rays having mean energy of 45 keV (70 kV + 0·5 mm Cu) by using a method for energy dependence calibration developed at the National Personnel Dosimetry Laboratory, Prague. Read-out was made with a Teledyne Isotopes 7100TS reader using pure nitrogen. The TLD's were annealed by a standard method including 24 hours at 80°C before irradiation. The standard deviation for one exposure measurement was less than ±5 per cent. The $^{99}\mathrm{Tc}^{\mathrm{m}}$ activities were calibrated in a Capintec well ionization chamber and had an estimated accuracy of better than ±5 per cent. According to our measurements of the energy dependence of TLDs the difference in their response to 20 keV and 140 keV photons of $^{99}\mathrm{Tc}^{\mathrm{m}}$ and that to calibration X rays is less than 10 per cent. This result is in agreement with data of Cameron *et al.* (1968).

The experimental results are shown in Table I together with values calculated by the methods of Henson (1973) and Hušák (1971). It can be seen that those due to Henson are in better agreement with experiment than those of Hušák, but both methods underestimate equally for the full 20 ml. syringe. Possibly, for this large syringe, some allowance is required for scattered radiation build-up, though this was omitted from all the calculations. A more complete picture is given in Fig. 1 which shows curves of the variation of surface exposure-rate with the volume injected. These were calculated by the method used by Henson and include a curve for a 1 ml. syringe (2·3 mm i.d., 3·3 mm o.d.) for which measurements were not made. Experimental points from Table I have not been added to the curves to retain clarity in the region where the latter are very close. Exposure rates, for example, for 5 ml. in 5, 10 and 20 ml. syringes are within ±5 per cent as a result of the geometries of the various source configurations. As small volumes are approached, the curves for 5, 10 and 20 ml. syringes approach asymptotically the value of exposure-rate from an infinitely thin disc source containing 1 mCi. In practice, of course, as the syringe is emptied the surface exposure rate R, in mR.min.$^{-1}$, falls to zero with decreasing volume according to $R = vCR_v$ where R_v is the exposure-rate per mCi at volume v ml. given by the appropriate curve, and C is the concentration of activity in mCi. ml^{-1}.

1976, *British Journal of Radiology*, *49*, 570–571

Correspondence

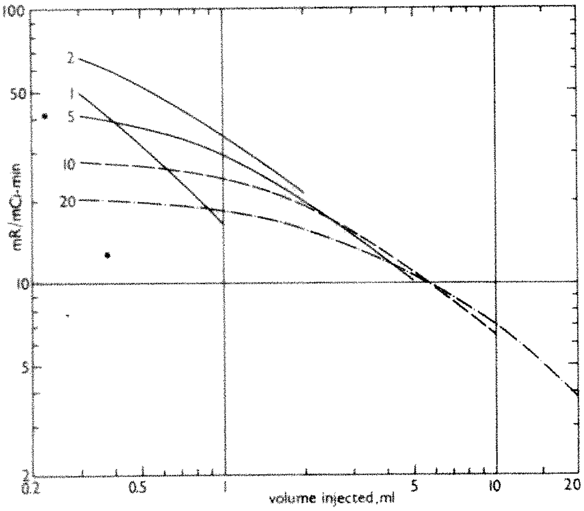

FIG. 1.

Calculated exposure-rates, mR.mCi^{-1}.min^{-1}, from ^{99}Tc^{m} in 1, 2, 5, 10 and 20 ml. plastic syringes.

TABLE I

COMPARISON OF MEASURED AND CALCULATED EXPOSURE RATES, mR/mCi-MINUTE

Syringe ml.	Volume injected ml.	Measured mR/ mCi-min.	Calculated	
			Hušák	Henson
2	2	20·0	17·3	21·1
5	5	10·2	9·4	10·2
10	10	7·0	6·1	6·5
20	20	4·5	3·9	3·9

The writers are satisfied with the agreement between their methods and note that the previous differences in results referred to above were due to the following:

1. Different values of exposure-rate constant were used. Hušák took 0·56 R.cm^2.mCi^{-1}.h^{-1} for the 140 keV γ rays. Henson used 0·58 R.cm^2.mCi^{-1}.h^{-1} for the γ rays and 0·18 R.cm^2.mCi^{-1}.h^{-1} for the 18–20 keV X rays (these values were also used in the present calculations).
2. A build-up function for scattered radiation using coefficients relating to a point source in an infinite water medium was incorporated by Henson in his calculation. It was noted that this would overestimate results for small syringes, but was justified by the aim of the paper in making estimates of skin doses for protection purposes. The build-up function resulted in about a 20 per cent increase in calculated exposure rates; it was excluded from the calculations reported here.
3. Results in Henson's paper were rounded to the nearest 5 mR.mCi^{-1}.min^{-1}, thus exaggerating in some cases the differences between the two authors. Also, Hušák's original work was with glass syringes with different dimensions, particularly wall thickness, from the plastic ones used by Henson.

Yours, etc.,
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REFERENCES

CAMERON, J. R., SUNTHARALINGAM, N., and KENNEY, G. N. 1968. Thermoluminescence dosimetry, p. 37 (University of Wisconsin Press).

HENSON, P. W., 1973. Radiation dose to the skin in contact with unshielded syringes containing radioactive substances. *British Journal of Radiology*, *46*, 972–977.

HUŠÁK, V., 1971. Exposure rate at the surface of syringes containing radioactive material. *Journal of Nuclear Medicine*, *12*, 574–575.

THE EDITOR—SIR,

RADIATION DOSE MEASUREMENTS TO THE EYES DURING CEREBRAL ANGIOGRAPHY

Recent interest in radiation dose to the cornea during neuroradiological investigations (Isherwood *et al.*, 1975) prompted us to test our own figures during cerebral angiography. Thermoluminescent dosemeters (TLD) appropriately marked right and left were placed over the eyes of patients undergoing cerebral angiography. Our equipment consists of 24 × 30 cm Puck film-changers with Siemens Special Super High Speed screens and a Siemens Tridoros 5S generator. Two X-ray tubes are in use: a Siemens high speed Bi 150/12/101R with 0·3 mm and 1·3 mm foci and a Rurek collimator for conventional angiography, and a Siemens Bi 125/4/7/50 RG with 0·1, 0·2, 1·0 mm foci and multi-leaf collimator for magnification angiography and screening. Kodak RPL film is used.

Conventional angiography only was used in Cases 1, 2 and 3; direct serial magnification angiography in Cases 4, 5 and 6 and a combination of conventional and magnification angiography in Cases 7 and 8. The results are presented in the accompanying table. The antero-posterior position (AP 12° ↓) in carotid angiography is taken with the X-ray tube angled 12 deg. towards the feet from the radiographic base line. In the vertebral angiogram, the antero-posterior position (AP) is taken with the chin raised, the radiographic base line at an angle of 35 deg. from the vertical and centred, with a straight tube, to the nasion, *i.e.* directly through the orbits. The right eye was nearer to the X-ray tube during all lateral exposures. In the lateral position for conventional angiography the focus/object distance refers to the distance from the focus to the median-sagittal plane, and in the antero-posterior position the distance from the focus to the coronal plane between the auditory meatuses. In magnification views the focus/object distance refers to the distance from the focus to that approximate area in the cranium under examination.

The results seemed to indicate:

(1) that the dose to the eye is chiefly dependent upon the number of Towne's and antero-posterior views;

(2) that in magnification angiography the region of interest strongly affects the radiation dose and it may be possible to minimize it at least on one side (Case 4) by coning down to the area of interest.

There are clearly strong grounds for using lead eye

			Exposure			Number of films in series	Focus/object distance cm	Degree of magnification	Dose received rad	
Case number	Vessel injected	Position	mA	kV	Time sec.				Right eye	Left eye
1	Left carotid artery	Lateral	400	58	0·1	11	90	Nil		
		A-P 12° ↓	400	63	0·12	10	90	Nil		
		Lateral neck	400	58	0·1	1	90	Nil		
		A-P neck	400	60	0·1	1	90	Nil		
		Lateral neck	400	62	0·1	1	90	Nil	5·07	3·61
2	Right carotid artery (with cross compression)	Lateral neck	400	60	0·1	1	90	Nil		
		Lateral	400	60	0·1	11	90	Nil		
		A-P 12° ↓	400	63	0·12	10	90	Nil		
		A-P 12° ↓	400	63	0·12	10	90	Nil	9·93	8·74
3	Left carotid artery	Lateral neck	400	58	0·1	1	90	Nil		
		Lateral	400	59	0·1	11	90	Nil		
		A-P neck	400	56	0·1	1	90	Nil		
		A-P 12° ↓	400	64	0·12	10	90	Nil	5·4	4·73
4	Left carotid artery	Lateral	100	77	0·32	7	50	1:2		
		Oblique	100	85	0·32	3	50	1:2		
		A-P 12° ↓	100	85	0·32	7	50	1:2	0·466	5·74
5	Vertebral artery	Lateral	100	70	0·32	8	50	1:2		
		Townes	100	80	0·32	7	50	1:2		
		A-P	100	80	0·32	7	50	1:2		
		Lateral (auto tomos)	100	80	0·32	7	50	1:2	3·57	3·11
6	Vertebral artery	Lateral	100	70	0·32	1	50	1:2		
		Townes	100	85	0·32	6	50	1:2		
		A-P	100	80	0·32	6	50	1:2		
		Lateral	100	70	0·32	6	50	1:2		
		Lateral	100	73	0·32	7	50	1:2		
		Lateral	100	73	0·32	7	50	1:2	3·35	3·2
7	Right carotid artery	Lateral neck	400	58	0·1	1	90	Nil		
		A-P neck	400	62	0·1	1	90	Nil		
		Lateral	400	63	0·1	11	90	Nil		
		A-P neck	400	62	0·1	1	90	Nil		
		Lateral neck	400	58	0·1	1	90	Nil		
		Lateral	125	78	0·32	6	50	1:3	5·55	0·44
8	Bilateral carotid arteries	Lateral	400	62	0·1	1	90	Nil		
		Lateral neck	400	60	0·1	1	90	Nil		
		Lateral	400	64	0·1	10	90	Nil		
		A-P neck	400	60	0·1	1	90	Nil		
		A-P 12° ↓	400	67	0·12	10	90	Nil		
		A-P oblique	125	76	0·32	6	50	1:2		
		Lat. oblique	125	65	0·32	6	50	1:2		
		Lat. oblique	125	65	0·32	6	50	1:2		
		Laternal neck	400	60	0·1	1	90	Nil		
		Lateral	400	64	0·1	10	90	Nil		
		A-P neck	400	60	0·1	1	90	Nil		
		A-P 12° ↓	400	67	0·12	10	90	Nil	15·2	11·3

shields of suitable design whenever possible. Fortunately one may always be worn for the "AP 12°" view.

Yours, etc.,
C. CHRISTINE SMITH,
H. S. WILLIAMS,
G. DU BOULAY.

The National Hospital,
Queen Square,
London WC1N 3BG.

REFERENCES

ISHERWOOD, I., YOUNG, I. M., BOWKER, K. W., BRAMALL, G. K., 1975. Radiation dose to the eyes of the patient during neuroradiological investigations. Congressus Tertius Societatis Radiologicae Europaeae. Edinburgh, 1975, and *Neuroradiology*, *10*, 137–141.

1976, *British Journal of Radiology*, *49*, 572

Correspondence

THE EDITOR—SIR,

THE 2,500 RET ENVELOPE

The results of treatment in cancer of the cervix vary widely around the world. Many reasons have been suggested to explain the discrepancies, including errors in staging and "personalization" of treatment.

Unfortunately, it has not been possible to make useful comparisons between different centres. This has been partly due to inadequate methods of describing dosimetry patterns in the pelvis. Prescribed doses are often close to the limits of tolerance. Enormous doses are delivered to the tissues next to the intracavitary applicator, but, due to the inverse square law, these doses fall off extremely rapidly over small distances. Thus it has been difficult to agree on a point which is clinically meaningful for prescription purposes.

The confusion is seen in several treatment situations. For instance, in endometrial carcinoma, some centres quote the uterine dose in milligram-hours, but the vaginal dose in rad. Where interstitial therapy is added, dosimetry by this means becomes very difficult if not impossible, even where sophisticated computer techniques are available. In describing a clinical example of such a case, the current edition of a well-known textbook (Fletcher, 1973) simply states "No attempt was made to calculate the implant".

The problem is further complicated by the difficulty of combining radium dosimetry and external dosimetry (Joslin *et al.*, 1972). It is sometimes felt that a radium rad is *physically* different from a megavoltage rad, and that adding the two units together is like adding "apples and pears". This may not be the case. The apparent clinical differences in dose tolerance are probably mostly due to the different volumes of tissue irradiated. A less important factor is the continuous low dose-rate effect of radium compared with intermittent fractionated external therapy.

Thus in the treatment of pelvic cancer, the delicate balance between morbidity and mortality depends as much on the volume of tissue irradiated as on the dose at a fixed point. I have recently analysed this factor and noted that if the treatment volume is decreased by 50 per cent, the tolerated dosage can be increased by 25 per cent in the pelvis (Lowry, 1973). Bolande (1971) suggested incorporating this factor and proposed quoting the volume enclosed by an envelope whose surface dose is about that of a point A, namely 7,000 rad.

In the final analysis, when we come to compare pelvic dosimetry in different centres, we will also need to know the fractionation used. The Manchester, Stockholm, Paris, Houston and other techniques all use different quantities of radium in different combinations with external therapy. It is now possible to compare these different fractionation schedules using the Ellis formula and ret system of dosimetry (Ellis, 1971). This concept can be extended to include intracavitary irradiation using an iso-effect link between continuous radium dosimetry and discontinuous external beam therapy. Applying this method, the nominal standard dose (NSD) at point A is about 2,500 rets (George, 1971).

We now have an opportunity after many years of combining all the above concepts on the computer and, at the same time, incorporating current concepts in radiation therapy and radiobiology. In most cases of malignant disease, a dose of 2,500 rets is lethal. It is therefore recommended that the volume of tissue enclosed in the 2,500-ret envelope should be quoted. Tissue within this envelope would receive a supralethal dose. Tissue outside would have the potential for sublethal recovery. The envelope itself would still be a "flat pear" whose "waistline" would lie somewhere near point A. Calculations suggest that the volume of this envelope varies between 100 cm^3 and 200 cm^3. The exact volume can be determined on the computer by integrating slices of tissue across a fixed plane.

The shape of the envelope will vary in different treatment situations. But the outline can be determined on the computer and the data displayed in the form of a computer print-out. It is then possible to sketch in the position of the tumour, bladder and rectum. Several examples of different treatment situations have been worked out in the United States and detailed results will be presented shortly.

Lastly it is noted that the 2,500 ret envelope incorporates time and is essentially a four-dimensional concept.

Yours, etc.,
W. S. LOWRY.

Department of Cancer Studies,
The Queen's University of Belfast.

REFERENCES

BOLANDE, J., 1971. Afterloading in radiotherapy. *Proceedings of Conference*, panel discussion, U.S. Department of HEW, New York.

ELLIS, F., 1971. Nominal standard dose and the ret. *British Journal of Radiology*, *44*, 101.

FLETCHER, G., 1973. *Textbook of Radiotherapy*, pp. 645 (Lea and Febiger, Philadelphia).

GEORGE, F. W., 1971. Afterloading in radiotherapy. *Proceedings of Conference*, p. 292, U.S. Department of HEW, New York.

JOSLIN, C. A. F., SMITH, C. W., and MALLIK, A., 1972. The treatment of cervix cancer using high activity 60Co sources. *British Journal of Radiology*, *45*, 257–270.

LOWRY, W. S., 1973. The volume factor in radiotherapy. *Proceedings of the XIII International Congress of Radiology, Madrid.*

THE EDITOR—SIR,

RENAL OPACIFICATION—MISLEADING ILLUSTRATION

In the most recently published volume of *Recent Advances in Radiology* (1975), Dr. T. Sherwood discusses the role of volume change in renal opacification. Based on his own illustrated experiments, he concludes that an increase in the amount of contrast medium alone, without a change in concentration, will not readily lead to a discernible radiographic density effect. We believe that changes in the amount of contrast medium play an important role in renal opacification under all the many urographic situations (Dure-Smith *et al.*, 1971; Dure-Smith *et al.*, 1974; Dure-Smith *et al.*, 1972; Dure-Smith, 1975; Dure-Smith *et al.*, unpublished), but particularly in obstructive uropathy (Dure-Smith *et al.*, 1972). On review of all the material, this difference of opinion seems to be more apparent than real, particularly as we have now had the privilege of seeing the original radiographs of Dr. Sherwood's experiments, and they bear little resemblance to the published illustrations. In fact these experiments confirm rather than conflict with our view. However, it is a pity that they are presented in this way in such a distinguished text-book since they appear to contravene several basic physical concepts and this may be misleading to those not conversant with the principles of X-ray imagery or the minutiae of this particular subject.

The experiments consist of radiographing four balloons filled with increasing volumes (2·5, 5, 10 and 20 ml.) of contrast medium containing 15mg/ml. of iodine in a water-bath 7·2 cm deep. A repeat experiment used a concentration of 150 mg/ml. of iodine.

The radiographs as published show no detectable difference between *any* of the balloons. This would imply that not only does volume change make no difference, but neither does a change in concentration from 15 to 150 mg/ml. of iodine (virtually the whole range occurring during urography). The original radiographs do show the expected difference between the two concentrations for all volumes.

The original radiographs do not, however, show a significant change in density with increasing volume. Nor is there a greater opacity in the centre of the balloon compared with the periphery. We have shown both these changes when we repeated these experiments using the same volumes and nominal radiographic factors but changing the concentrations. This we believe is the crux of the matter—that there is an optimal range of concentrations for any given depth of contrast medium (Dure-Smith *et al.*, 1974; Dure-Smith *et al.*, unpublished). The two concentrations (15 and 150 mg/ml. iodine) chosen by Dr. Sherwood happen to fall outside this optimal range. Even within the optimal range changes in film density are small and depend not only on radiographic factors, but also on the characteristics of the film and processing. If the image of the smallest volume or depth appears white, increasing either depth or concentration will produce no discernible effect. Sherwood's illustration using 150 mg/ml. is correct in this respect, but the illustration using 15 mg/ml., apparently also showing no effect, is incorrect as his original radiograph shows, in that the balloons were only just opaque and not white. In this low film-density range a change of concentration × 2·4 or depth (2·5–20 ml. sphere) we would expect to produce a virtually undetectable change in density. We have previously pointed out (Dure-Smith, 1974) that this has a practical application in patients with renal impairment who can achieve only low concentrations of contrast medium in their urine; they are doubly disadvantaged in that they need much larger changes in both depth and concentration of contrast medium to produce a detectable improvement in opacification.

This subject has also been confused by the semantics of biological shapes; whether the nephrons or calyces present spheres, ovoids or cylinders to the X-ray beam and the effects which such shapes have on the depth/volume ratio. However, it matters little what the exact shape is providing, as we believe, it is capable of a significant change in depth. We abandoned our biological shaped model because there is so little control over the shape it assumes (and hence depth of contrast medium). Further, the smallest volume (2·5 ml.) chosen by Dr. Sherwood must surely represent a rather hydronephrotic calyx, and its relevance to the normal calyx must be limited in view of the critical depth/concentration relationship.

We feel the discussion has moved on since this chapter in *Recent Advances* was written and the question is not now whether or not there are significant depth changes but what contribution they make to renal opacification for any particular concentration of contrast medium.

We are very grateful to Dr. T. Sherwood for allowing us to see one of his original radiographs. We would also like to thank Dr. P. Winstanley, Principal Pharmacist to the Radcliffe Infirmary, for dispensing the correct concentrations of the contrast medium, and to Miss Wendy Hills, D.S.R., for radiographic assistance.

Yours, etc.,
P. Dure-Smith,

Department of Radiology,
Thomas Jefferson University Hospital,
Philadelphia 19107, U.S.A.
(Visiting Fellow, Wolfson College 1974–75.)

G. M. Ardran.

Nuffield Institute for Medical Research,
University of Oxford, 43 Woodstock Road,
Oxford OX3 6HF.

REFERENCES

Dure-Smith, P., Simenhoff, N., Zinskind, P. O., and Koproff, M., 1971. The bolus effect in excretory urography. *Radiology*, *101*, 29–34.

Dure-Smith, P., Simenhoff, M., Brodsky, S., and Zinskind, P. D., 1972. Opacification of the urinary tract during excretory urography: concentration vs. amount of contrast medium. *Investigative Radiology*, *7*, 407–410.

Dure-Smith, P., Rosen, R., Stern, A., Fraimow, H., and Simenhoff, M., 1974. Physiology of the excretory urogram III. A densitometric and subjective assessment of changes in contrast medium concentration. *Investigative Radiology*, *9*, 104–108.

Dure-Smith, P., 1974. Excretion of contrast medium. *British Journal of Radiology*, *47*, 825–826.

Dure-Smith, P., Rosen, R., Fraimow, H., and Galkin, B. Physiology of excretory urography V. The role of volumetric changes in urinary tract opacification (unpublished).

Sherwood, T., 1975. The urinary tract. In *Recent Advances in Radiology*, *5*, edited by T. Lodge and R. E. Steiner, pp. 247–262.

The Editor—Sir,

Must Radiologists do all the Reporting?

Your Editorial in July asks if radiologists must do all the reporting, and you publish a letter from Dr. Emrys-Roberts.

With an increased work-load and a shortage of radiologists, the ideal of reporting on all X-ray examinations is one few of us can accomplish. Indeed, it is foolish to try. It results in reporting at too fast a rate, leading to an increase in errors and distortion of the work pattern as too little time is available for lengthy specialized procedures. Today, many films have to pass through X-ray departments unreported, the type of case varying from hospital to hospital and with the working agreements of the clinicians concerned.

We must accept the fact that the ideal of radiologists seeing all films cannot be achieved with the present workload. The answer lies in compromise and probably some combination of the following:

1. The curtailment of the number of investigations depending on the diagnostic yield in a given clinical situation (several papers on this have been published), and the limitation of investigations so they provide only the answers to the questions posed by the clinicians.

2. Getting help from other doctors. This will mean two levels of skill, but this applies to most branches of medicine. A radiologist should be available to help with problems.

Off-loading work to community hospitals is a further step which is less secure. The diagnostic yield from examinations undertaken in departments outside the supervisory umbrella of a radiologist will be less and the radiation to the patient probably more. The small department will not be used to capacity, giving a greater cost per examination.

3. Assistance under (2) is likely to be limited, but I believe radiographers could help. With non-contrast studies, suitable radiographers should be able to place films in three categories, "normal", "probably normal" and "abnormal". (I include "probably normal" to avoid the problem of the borderline cases and radiographers exceeding their knowledge to avoid having to put "normal" cases in the "abnormal" category.) The radiographers would issue a "normal" report, signing it themselves. I know this is against the Articles of The Society of Radiographers and has medico-legal implications.

With follow-up cases, radiographers should be able to place examinations in three categories, "better", "the same" or "worse" with a view to reporting on those improving and long-term static cases.

Even more controversial, but with some advantages, radiographers may prove able to report on some or all casualty patients.

These ideas must cause conscientious radiologists concern but some compromise must be reached if radiology is to play its proper part within the present financial limits and shortage of radiologists.

Yours, etc.,
K. R. Aberdour.

270, Springfield Road,
Chelmsford,
Essex CM2 6AS.

1976, *British Journal of Radiology*, 49, 574

Correspondence

THE EDITOR—SIR,

MUST RADIOLOGISTS DO ALL THE REPORTING?

In reply to your editorial, I believe it is undesirable for radiographs to be seen by clinicians or casualty officers alone and not by radiologists.

However, owing to the poor prospects in consultant work in radiology in particular, it seems inevitable that many films will not be seen by radiologists in the future.

With regard to community or cottage hospitals, I have had some experience. Where there was an open department and no radiologist present, frequently the radiographer would be inundated with requests and patients, often sent up by ambulance without an appointment. Furthermore, the radiographer was regularly asked for her opinion on a film—a highly unsatisfactory procedure.

If X-ray facilities are established in community or cottage hospitals and the radiologist is unable to report on films because of pressure of work, two points should be noted: first, no radiographer should be expected to give an opinion since this is an unfair responsibility and secondly, the radiologist should take no responsibility for the department in any way whatsoever.

Yours, etc.,
G. A. MEDHURST.

Consultant Radiologist,
Kettering and District General Hospital,
Rothwell Road, Kettering,
Northamptonshire NN16 8UZ.

THE EDITOR—SIR,

MUST RADIOLOGISTS DO ALL THE REPORTING?

I am writing to you concerning your editorial which has recently come to my attention together with the letter which appeared in your columns from the Chairman of the Association of General Practitioners' Hospitals in the same issue of July, 1975.

I think that radiologists should as far as possible view all of the X rays carried out in the hospitals under their administration, as I regard the maintenance of radiographic standards to be one of the main duties of the radiologist. It is obviously not practical nor essential for radiologists to report on, for instance, follow-up chest films from a chest clinic or dental X rays.

It has taken a long time for radiology to become accepted in this country in the same way that it has in Scandinavia and in the United States. It would be a retrograde step for radiology to have multiple small X-ray departments in community hospitals once more scattered over the country without adequate radiological control to ensure high standards. I note that in his letter Dr. Emrys-Roberts states that in some hospitals he would anticipate X-ray facilities of wide capability. I took this to mean that he might envisage the use of contrast examinations, particularly urograms being carried out without the presence of a radiologist. This would also imply the provision of tomography in some instances. I regard this particularly to be condemned.

Despite the objections of the radiologists, however, it is quite possible that it is the intention of the D.H.S.S. for political purposes to divert capital away from the district general hospitals into the community hospitals. Whilst consultant radiologists should continue to act in a consultative capacity it would appear to be dangerous for us to assume any administrative obligations to the community hospitals in view of the probable poor standards which would occur. The reason for my opinion stems from the wording of the Code of Practice 2.1.2 which might make the consultant radiologists liable for any accidents which may occur with the use of radiological equipment if he is in administrative charge.

Yours, etc.,
K. GRAINGER.

X-ray Department,
The Ipswich Hospital,
Anglesea Road Wing,
Ipswich, Suffolk IP1 3PY.

THE EDITOR—SIR,

MARKING OF LATERAL CHEST FILMS

One method of marking films is to imbed permanently in the front face of every cassette a small radio-opaque marker—a flattened lead-shot is very convenient. If the cassette is held upright, resting on a short side, and the marker is placed one-third of the distance down the right-hand side, the tube side of every film exposed in such a cassette is automatically indicated because the film must be held so that the image of the marker appears one-third of the way down the long right-hand border.

This unobtrusive method has the advantage that it does not require the attachment of any additional marker by the radiographer. It does, however, require knowledge of the patient's position relative to the tube, that is, facing towards, or away.

Yours, etc.,
A. P. ALLEN.

109 Powderham Street,
New Plymouth,
New Zealand.

(*Editors' note*: This correspondence is now closed).

1976, *British Journal of Radiology*, *49*, 575

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meetings announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

Computers in Radiotherapy in Europe

It is proposed to hold a Workshop at IAEA, Vienna, on July 5–10, 1976, organized by the Groupe Informatique, A.E.R. with the support of the European Association of Radiology. The aim will be to establish the contribution that the computer makes at the clinical level in the fields of dose computation, clinical records, radiobiology, etc., and to determine future developments.

Further information from Dr. D. N. Edwards, Clinical Research Unit, Mersey Regional Centre for Radiotherapy and Oncology, Clatterbridge Hospital, Bebington, Wirral, Merseyside L63 4JY, U.K.; or Dr. T. Moller, Radioterapikliniken, Lasarettet, S–221 85 Lund, Sweden.

First Meeting of the World Federation of Ultrasound in Medicine and Biology

This meeting, to be held August 3–7, 1976 in San Francisco is the third world congress on ultrasonics in medicine.

Reduced registration fees are payable by members of the international sub-group of the British Medical Ultrasonics Group.

Further information from: 1st W.F.U.M.B., PO Box 25606, Oklahoma City, Oklahoma 73125, U.S.A.

For information above B.M.U.G. contact the General Secretary, B.I.R., 32 Welbeck Street, London W1M 7PG.

A Symposium on Radioisotopes in Cardiology

Jointly organized by The British Institute of Radiology and the British Cardiac Society will be held on Wednesday, September 29, 1976, at the Greenwood Conference Centre, Guy's Hospital.

A review of the present position will be given by U.K. and overseas speakers. A limited time will be allocated to original presentation for which abstracts in not more than 200 words should be submitted by June 30.

Registration fee: £9·50 including lunch, morning coffee and afternoon tea.

Further details and registration forms will be available from The Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Attendance may be limited and registrations will be accepted in the order they are received.

8th Congress of the Society of Hungarian Radiologists and 12th Annual Meeting of the European Society for Radiation Biology

To be held in Budapest, Hungary, October 19–22, 1976.

For further information please contact the Congress Office (H-1361 Budapest, PO Box 32, Hungary).

Radiation Protection: An Example of Action Against Modern Hazards

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P. no. 33, 92260 Fontenay-aux-Roses, France.

Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV International Congress of Radiology

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colégio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Book reviews

Report of the Task Group on Reference Man. ICRP Publication 23. A report prepared by a Task Group of Committee 2 of ICRP, W. S. Snyder (Chairman) M. J. Cook, L. R. Karhausen, E. S. Nasset, G. Parry Howells, I. H. Tipton, pp. 480, 133 tables, 83 illus., 1975 (Oxford, Pergamon Press), £21·50.

Just 25 years ago, in January 1951, this Journal published the current recommendations of the International Commission on Radiological Protection. That document of eight pages included a four-page supplement on "Maximum Permissible Amounts of Radioactive Isotopes" (ten were considered) with a two-and-a-half page appendix on Standard Man—mass of organs, chemical composition and applied physiology. Reference Man is a descendant from his puny predecessor, via two more extensive reports in 1954 and 1959, but it is reassuring to know that he still weighs 70 kg, and his thyroid 20 g, although his liver and pancreas have enlarged from 1,700 to 1,800 and 70 to 100g respectively, and his brain has shrunk from 1,500 to 1,400 g.

Reference Man is in this report defined as being "between 20–30 years of age, weighing 70 kg, is 170 cm in height, living in a climate with average temperatures of from 10° to 20°C. He is a Caucasian and is a Western European or North American in habitat and custom". Although not discussed in the introduction the detailed tables make clear that he has a reference mate who weighs 58 kg and is 160 cm high (reassuring in International Women's Year).

This impressive, extensively researched work contains, of course, far more than a simplified catalogue of single standardized values for the constituent parts and functions of an arbitrary average man. The report is divided into three major sections: I. Anatomical values (229 pages), II. Gross and elemental content (59 pages), and III. Physiological data (84 pages) for Reference Man, with appendices, an extensive index and over 1,600 references (all including the titles of papers cited). Sections on the anatomical values for individual organs cover, in critical discussion, such items as weight, general description, volume, specific gravity, volume of blood, tissue growth. The section on elemental content considers 51 elements, generally those also dealt with in this report's immediate predecessor, the 230-page Report of Committee II on Permissible Dose for Internal Radiation, 1959; however, in contrast to the 1959 report, here the available data are sifted and discussed, and where data are scarce, widely varying or non-existent, this is pointed out. It is for example noted firstly that "published values for the concentration of cobalt in supposedly normal human tissues vary widely—as much as a thousand fold", and secondly, that the source of these discrepancies was almost certainly the contribution by cobalt from the glass containers used by some investigators. Well-planned tables cite, so far as practicable, the chief sources of data, the analytical methods used and the number of subjects considered.

These same 51 elements are considered in the third major section on physiological data. The authors have evidently made an heroic survey of the available literature, sifting data from some unlikely sources as well as the studies of well-known research workers in the field of radioactive tracer studies and activation analysis. "Zinc metabolism of young college women on self-selected diets", "Trace elements in humain hair", "^{210}Po in man", and so on through the 1,600 references.

An appendix by Walter Snyder oddly titled "Specific absorbed fractions of photon energies for Reference Man", presents some new calculations of dose for internally distributed photon emitters, using Reference Man values for organ masses, in place of those adopted in the earlier MIRD (1969) report by Snyder and colleagues and, also, where appropriate, by integration of build-up factors instead of Monte Carlo methods.

In the introduction, the authors stress that this is a "Reference Man for Radiation Protection" or "for Dosimetry", and the use of reference man data will serve the same roles, on a more extended scale, as the earlier Standard Man, *i.e.* to help in distinguishing experimental causes of differences in dose estimates from those due to essentially arbitrary differences in anatomical or physiological assumptions; and generally, to reduce the labour of performing and reporting such dose calculations, by using this Report as a main reference.

The report is intended primarily for the "Health Physicist" making calculations of dose from internally distributed radionuclides. With the rich documentation provided he will undoubtedly find much more scope here for exploration in depth of the consequences of various patterns of distribution, although, as stated earlier, in the summarized simplified values for individual organs there is often little variation from the previous report.

As an intellectual exercise the report is undoubtedly impressive if, inevitably for its size and scope, expensive. Yet one must realize that it still represents only a part, if a vital one, of the area of work covered in the full Committee II reports of 1954 and 1959; there are no tabulations similar to those provided in the 1959 Committee II Report of the kinetics of individual radionuclides, although the detailed physiological data can form the basis for the preparation of such tables.

The production and layout of the book are of high quality. Clearly an essential work for the library of any institution concerned with the evaluation of radiation dose.

N. G. Trott.

Radiology of the Skull and Brain. General Angiography—Volume II. Edited by T. H. Newton and D. G. Potts (Book 1: *Technical Aspects;* Book 2: *Arteries;* Book 3: *Veins;* Book V: *Specific Disease Processes*), pp. 2,786, 1974 (London, Henry Kimpton), £99·35.

This detailed account of cerebral angiography is divided into four books, comprising 47 chapters, each contributed by a leading neuro-radiologist, expert in the subject being discussed. Despite the total of almost 2,000 pages and the multiple authors involved, there is very little unnecessary repetition and continuity is good.

Each chapter gives a complete, well written, up-to-date account of its subject, frequently with original contributions and with a relevant selection of illustrations including many excellent subtracted angiograms.

The first book discusses and describes in detail the techniques of modern neuroradiology. The second and third are devoted to detailed accounts of the anatomy including the embryology of the individual vessels and how they are affected by the various pathological processes. Book 4 deals with the angiographic features of particular disease processes giving emphasis to their pathological appearances rather than their effects in particular regions.

The work is beautifully produced and there is a comprehensive index. It is an excellent reference book for all neuroscientists and should remain so for the foreseeable future.

B. Kendall.

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Printed in Great Britain by Lund Humphries
London and Bradford
Published by THE BRITISH INSTITUTE OF RADIOLOGY
32 Welbeck Street, London W1M 7PG

ISSN 0005-1285
08440